9.1 Introduction

This chapter is a continuation of Chap. 8 focusing not only on traumatic but also on nontraumatic solid organ injuries, including drug-induced organ toxicity and intoxications, all of which are known to be associated with the emission of pathogenetic DAMPs. These molecules—in case of an infectious injury together with MAMPs—can trigger acute uncontrolled/dysregulated proinflammatory processes, clinically manifested as an acute organ-specific disease. Eventually, in case of acute repetitive or persistent injuries, tissue inflammation transitions—via chronic nonresolving inflammation and under involvement of MAMP/DAMP-promoted profibrotic pathways—into chronic organ fibrosis, often clinically manifested as chronic organ failure (for global DAMP-induced inflammatory and fibrotic responses, also compare Vol. 1, [1], Part VI, Sects. 22.2.4 and 22.2.5, and Part VIII, Sect. 36.4). Here, some major organ-specific injuries have been selected, restricted to the brain, lung, kidney, liver, pancreas, and musculoskeletal system but all emphasized in light of the danger/injury model in Immunology.

In addition, given some peculiarities of intoxications per se and excessive alcohol consumption as a global healthcare problem, in particular, the alcoholic intoxication has been chosen as a typical acute injury affecting many tissues and organs, including the brain, liver, and pancreas. From the perspective of the book, a few aspects are touched to this kind of organ damage by highlighting the role of DAMPs again.

9.2 Brain Injury

9.2.1 Introductory Remarks

Neuroinflammation is defined as the homeostatic or dysregulated innate immune response of the CNS against cell stress and tissue injury. The neuroinflammatory
response presents shared characteristics with peripheral inflammation but also retains specific features, such as the existence of the blood–brain barrier (BBB) and the cerebrospinal fluid (CSF), or the activation of PRM-bearing glial cells. Etiologically, several brain injuries are known to induce neuroinflammation, including TBI, cerebral stroke, bacterial and viral infections, and alcoholic intoxication. Here, a few remarks are made restricted to TBI and alcohol intoxication.

9.2.2 Traumatic Brain Injury

Etiologically, the most important variants of neuroinflammation-inducing injury are traumatically acquired brain injuries that are clinically grouped by severity: mild, moderate, and severe injuries [2]. The severe acute TBI—a leading cause of death and disability worldwide—is a heterogeneous disorder resulting from an external force applied to the head. The TBI triggers a focal immune response that is initiated within minutes after the primary injury. This focal brain inflammation involves both brain-resident and peripheral immune cells with complicated interactions. Typically, the development of cerebral edema (CE) plays a central role in the evolution of this particular injury and is closely associated with pathoneurological outcomes (for reviews, see [3, 4]). Current notions hold that TBI promotes a robust innate immune response induced by DAMPs that are also denoted as immunological stressors elsewhere [5, 6]. In the following, the emerging evidence and features of focal brain inflammation after TBI are briefly outlined by highlighting the pathogenetic role of DAMPs.

9.2.3 Regulated Cell Death in Traumatic Brain Injury

As experimentally shown, various subroutines of RCD reportedly occur in TBI including apoptosis [7], necroptosis [8–10], ferroptosis [11–15], and pyroptosis [16, 17] (for RCD, see Sect. 4.3 and Vol. 1 [1], Part V, Chap. 19).

The subroutine of ferroptosis has been uncovered to play a vital role in TBI. In fact, besides nonenzymatic oxidation mechanisms contributing to the overall oxidative burden immediately following brain injury, subsequent action of upregulated enzymes causing lipid peroxidation has recently been described, including members of the COX family, LOX family, and cytochrome P450 [18–20] (for mechanisms of lipid peroxidation-associated ferroptosis (compare Sect. 4.3.4.2 and Vol. 1 [1], Part V, Sect. 19.3.3 and Fig. 19.6).

Given the impact of these pro-oxidative processes in TBI (also see below), the detection of ferroptotically dying neurons is not surprising. For example, in a pediatric rat controlled cortical impact model of TBI, elevated levels of oxidized polyunsaturated PE lipid species could be detected at early time points (1–4 h) post-injury, consistent with the loss of GPX4 function and initiation of ferroptotic cell death [21]. In other studies on a controlled cortical impact model of TBI in mice, a loss of iron-positive cells and morphological evidence consistent with
ferroptosis (i.e., shrunken mitochondria) were observed at or near the injury site [14]. Moreover, in these experiments, cell death and the associated long-term motor and cognitive dysfunction were reduced by co-treatment with ferrostatin-1, an inhibitor of ferroptosis, administered at the time of injury directly into the cerebral ventricles.

In sum, these first observations suggest RCD to serve as critical sources of DAMPs, which trigger necro-neuroinflammatory responses involved in the pathogenesis of TBI, although the underlying molecular mechanisms are still not fully understood.

9.2.4 Pathogenesis of Traumatic Brain Injury (in Brief)

9.2.4.1 General Remarks
The pathophysiology of TBI is dominated by a complex dynamic process that initiates a multitude of cascades of pathological pathways, including alterations in cerebral perfusion, activation of inflammatory cytokines, and excitotoxicity (i.e., overactivations of receptors for the excitatory neurotransmitter glutamate, such as the N-methyl-d-aspartate [NMDA] receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptor). Its symptomatic presentation varies with each individual, injury type, injury severity, age, and gender. The complexity of the process results from primary and secondary brain injuries that result in temporary or permanent neurological deficits. The primary injury of TBI causes direct damage to neural tissue and refers to insults incurred from external mechanical forces of trauma that are regarded as the major factor determining the patients’ outcomes. Focal intracranial hemorrhage, epidural and subdural hematoma, brain concussion, and direct axonal damage are all examples of primary lesions that reflect primary sources of constitutive and inducible DAMPs (for pathologies induced by primary brain injury in TBI, see also [22]). Subsequently, a cascade of secondary injury processes (i.e., delayed nonmechanical damages) is initiated at the time of the insult and develops posttraumatically—from minutes to days from the primary impact.

9.2.4.2 Main DAMP-Triggered Pro-oxidative and Proinflammatory Processes Involved in the Pathophysiology of Traumatic Brain Injury
The subsequent injury is of essential pathophysiological importance. This injury is caused by multiple interconnected molecular pathways including but not limited to alterations in cerebral perfusion, ion/fluid imbalance such as calcium and iron perturbations, ROS-mediated oxidative stress, disruption of the BBB, mitochondrial dysfunction, excitotoxicity, and a neuroinflammatory response comprised of local and systemic immune activation (for in-depth articles, see [4, 23–30]). Oxidative stress is of particular relevance. As emphasized [31], excessive glutamate at the synaptic junction, which in turn activates its NMDA and AMPA receptors, facilitates excessive calcium influx into the neuronal cells and promotes oxidative stress
that further leads to mitochondrial dysfunction, oxidation of lipids, proteins, and DNA.

All these pro-oxidative and proinflammatory processes converge to and culminate in cell death pathways resulting in death of cerebral cells (Fig. 9.1). These cells are all susceptible to traumatic injury, with neurons being the most sensitive to direct injury, followed by oligodendrocytes, astrocytes, microglia, and ECs being particularly resistant to damage. As experimentally shown, various forms of cell death may occur, executed either directly via ACD or indirectly through RCD, as mentioned above. With the discovery of these subroutines of RCD, the critical sources of secondarily emitted DAMPs in TBI became evident, that is, DAMPs that are released from the damaged meninges, glial limitans, and parenchyma. Indeed, there is growing evidence in support of the notion that the emission of DAMPs that is associated with the various forms of TBI-induced neuronal cell death not only initiate but also perpetuate innate immune “cell death” pathways involved in the pathophysiology of TBI [25, 32, 33] (Fig. 9.1). These DAMP-promoted innate immune inflammatory responses, including complement activation, lead—or at least contribute—to CE that (1) plays a vital role in the evolution of injury following brain trauma, (2) is closely associated with neurologic outcomes, and, most importantly, (3) can lead to intracranial hypertension. Indeed, it is this intracranial

---

**Fig. 9.1** Simplified schematic diagram of a conceptual model illustrating emission of constitutive and inducible DAMPs during primary and secondary brain injury in TBI. Emission of DAMPs as a cause of external mechanical forces of the initial trauma promotes innate immune pro-oxidative and proinflammatory processes, which converge to and culminate in cell death pathways resulting in various subroutines of regulated necrosis (apoptosis → secondary necrosis, necroptosis, pyroptosis, ferroptosis). These various forms of regulated necrosis serve as secondary sources of emission of constitutive and inducible DAMPs, which, again, promote cell death pathways resulting in subroutines of regulated necrosis (i.e., a vicious circle of DAMPs emission). In severe trauma, these processes may lead to irreversible brain death. Note: compare also Sect. 4.3 and Fig. 4.2a, b and also Vol. 1 [1], Part V, Sect. 19.3, and Figs. 19.2, 19.4, 19.6, and 19.7. **PRM** pattern recognition molecules. (Sources: [4, 7–14, 16, 17, 23–30])
hypertension that can compromise cerebral perfusion pressure and cerebral blood flow, which can eventually cause irreversible brain injury, herniation, and death (for reviews, see [27, 34–36]).

9.2.4.3 SAMP-Promoted Inflammation-Resolving Processes in Traumatic Brain Injury

A resolution phase of the inflammatory response has been reported but does not always occur following TBI, and, thus, chronic inflammation can persist. Indeed, monocytes were shown to convert into macrophages that have the ability to produce neuroprotective cytokines (IL-10, TGF-β) in response to DAMPs. These macrophages are implicated in the cleanup of debris and damaged cells. Studies have also shown other beneficial aspects of cerebral immunity following brain injuries, besides resolution of inflammation, preservation of barrier function, and the release of trophic factors (for review, see Jassam et al. [27]). However, little is known regarding the role SAMPs in the resolving phase after TBI; nevertheless, a few SAMPs such as LXs, Rvs, and Pds have been described and will be briefly touched below.

9.2.4.4 Concluding Remarks

Together, modern insights into pathogenetic mechanisms of TBI have revealed a pivotal role of DAMPs that are implicated in various brain injury-induced neurological pathologies, including excitotoxicity, development of edema, and neuroinflammatory activities. Of note, in addition to focal brain inflammation, accumulating evidence obtained from patients and animal models suggests that brain inflammation after TBI is not restricted to the lesions but instead disseminates to areas remote from the lesions. Furthermore, the disseminated brain inflammation may be persistent and impact brain pathology, causing progressive neurodegeneration [30].

Histopathologically, various DAMPs reportedly induce proinflammatory activation in microglia, astrocytes, and neurons [37–40]: a topic that will be further explored below.

9.2.5 Alcohol-Related Brain Injury

Excessive, acute repetitive, and chronic alcohol consumptions are associated with the induction of a neuroinflammatory response in the brain that may contribute to neurodegeneration. Of note, as seen in other forms of injury, heavy alcohol intake, such as binge drinking, was observed to induce necrosis associated with neurodegeneration. Most commonly, long-standing heavy alcohol abuse leads to disproportionate loss of cerebral white matter and impairments in executive function (for reviews, see [41–44]).

Acute effects of alcohol on the CNS are mainly caused by injurious alcohol poisoning leading to encephalopathy, whereas chronic alcohol abuse is known to have long-lasting adverse effects on brain function and produce deficits ranging from mild cognitive impairment to dementia. The spectrum of dementias encompasses
Various pathophysiological mechanisms of alcohol-induced injury have been described, including inflammation, impaired anabolic signaling, upregulation of catabolic processes, and dysregulation in lipid metabolism. Current notions hold that alcohol-related metabolic encephalopathy is mediated by a self-perpetuating injury loop initiated by astrocyte swelling, which leads to oxidative and nitrosative stress, impaired intracellular signaling, PTMs of proteins, and gene expression (reviewed in [44, 47, 48]).

9.2.6 DAMPs in Brain Injury

9.2.6.1 General Remarks
As reported, both primary and secondary injury in TBI results in the release of DAMPs such as HMGB1, DNA and RNA, S100 proteins, ATP, uric acid, LPLs (i.e., inducible IIIB-5 DAMPs, a major phospholipid component of OxLDL), and lipid peroxidation-derived carbonyl adducts of proteins. Other critical sources of DAMPs refer to simultaneously occurring extracerebral organ injuries. For example, in studies in mice, bone fracture-stimulated emission of HMGB1 was shown to contribute to the development of secondary TBI [49]. Subsequently, DAMP-activated innate immune cells such as glial cells, neurons, leukocytes, and ECs produce inducible DAMPs including TNF and IL-1β which drive and expand early posttraumatic neuroinflammation (reported in [26, 27, 50–53]). Of note, the proinflammatory TNF was demonstrated to be linked to brain edema, BBB disruption, and recruitment of leukocytes, whereas the antiinflammatory IL-10 was assumed to possess neuroprotective properties [26, 54].

9.2.6.2 High Mobility Group Box 1
High mobility group box 1 has been described in Vol. 1 [1], Part IV, Sect. 12.2.2, denoted as a constitutive IA-1 DAMP, and Sect. 14.3.3, denoted as an inducible IIIB-2 DAMP (compare Table 3.1). The role of HMGB1 in TBI has recently been reviewed by Parker et al. [55]. So far, six studies have assessed the role of HMGB1 in TBI using mouse or rat models [56–61]. In sum, HMGB1—suggested to be released by injured necrotic neurons into the extracellular space—was shown to be involved in both early and later stages after TBI [57], and experimental inhibition of this IA-1 DAMP expression proved to be beneficial.

For example, in studies in rats, administration of an anti-HMGB1 mAb after TBI was shown to remarkably inhibit fluid percussion-induced brain edema [56] (for details, see Sect. 9.9.3.2). In contrast, intravenous injection of recombinant HMGB1 dose-dependently produced the opposite effects. Further experiments suggested the involvement of RAGE as the predominant receptor for HMGB1. In other lines of studies, ethyl pyruvate was shown to have protective effects on the development of CE following TBI in rats suggested by the authors to be mediated by the reduction
of HMGB1-triggered TLR4 → NF-κB signaling pathway [58]. In support of these findings were other lines of studies on a murine TBI model demonstrating that HMGB1 promotes CE via activation of TLR4 [59]. In two separate studies exploring potential therapeutic options, the neuroprotective agent glycyrrhizin was observed to (1) reduce CE significantly, (2) suppress the increase in BBB permeability and impairment of motor functions, and (3) improve outcomes in rats following TBI by downregulation of HMGB1-triggered, TLR4 or RAGE → NF-κB-mediated inflammatory responses in the injured rat brain [60, 61]. Together, these experimental studies in rodents significantly show that, following TBI, HMGB1 is released from damaged and necrotic neurons to trigger efferent innate immune pathways contributing to CE and other typical pathological features of this life-threatening organ injury.

Of note, there are a few reports on a role of DAMPs, in particular, HMGB1, in mounting a neuroinflammatory milieu in alcohol-induced brain injury (also compare [62]). For example, in rats, alcohol exposure during adolescence was found to activate HMGB1 → TLR4 signaling in the brain, and this activation was observed to persist into adulthood correlating with adult neurocognitive dysfunction [63]. In other lines of studies on mice, chronic alcohol treatment was shown to increase HMGB1 in cortex and cerebellum [64]. Also, as demonstrated by experiments in rats exposed to intragastric binge ethanol administrations, HMGB1 was found to be upregulated in the frontal cortex of the animals. In support of such findings are in vitro experiments on human and rat neurons, showing that ethanol can directly induce HMGB1 release in neuronal cells, associated with nicotinamide adenine dinucleotide phosphate-dependent oxidase 2 (NOX2)/NLRP1 inflammasome signaling [65].

The impressive findings of a pathogenetic role of HMGB1 in experimental TBI are reflected by clinical observations too. So far, four reports of investigating this DAMP in patients with TBI have been published [57, 59, 66, 67]. As competently summarized by Parker et al. [55], immunohistochemical examination of HMGB1 expression in brain tissue taken postmortem from patients with TBI showed immunoreactivity to be either lost or translocated to the cytoplasm of intralesional cells up to 1 day following injury. In cases resulting in death between 2 and 20 days post-TBI, HMGB1 was localized in the cytoplasm of infiltrating phagocytic microglia. Importantly, levels of HMGB1 could be measured in the CSF of adult patients with TBI [59] whereas, in pediatric patients, the CSF levels of HMGB1 were found to be even predictive for outcome [67]. Indeed, the detection of HMGB1 in the CSF indicates that this DAMP is released from injured neurons following TBI in humans. Moreover, an observational clinical study in patients with severe TBI revealed that the plasma HMGB1 concentration can be successfully used as a novel biomarker for significantly predicting 1-year mortality and unfavorable outcome of TBI [66].

Of interest in this context are clinical studies providing similar data in individuals with excessive alcohol consumption. Thus, young female regular alcohol binge drinkers reportedly show elevated HMGB1 in plasma [68], and—as revealed by postmortem brain studies on human alcoholic patients, who averaged over ten drinks per day with lifetime consumption of over 500 kg of alcohol—the expression
of HMGB1 was found to be increased in the frontal cortex of those patients [64]. Moreover, in similar analyses of human postmortem samples of the orbitofrontal cortex, the RAGE receptor was found to be upregulated in the postmortem human alcoholic orbitofrontal cortex, and an earlier age of drinking onset could be demonstrated to be correlated with increased RAGE, TLR4, and HMGB1 expression [69]. Given these data (and other data not quoted here), the authors concluded that “these data reveal that early life insults exert long-lasting neuroimmune changes in the developing CNS that might contribute to increased risk of developing alcohol dependence and other psychopathologies.”

Together, these clinical studies demonstrate increased circulating levels of HMGB1 in plasma or CSF of patients with TBI or increased alcohol consumption, suggesting this IA-1 DAMP to contribute to the pathogenesis of TBI and alcoholic brain diseases including Wernicke-Korsakoff syndrome and alcoholic dementia.

### 9.2.6.3 Mitochondrial DNA

Mitochondrial DNA has been described in Vol. 1 [1], Part IV, Sect. 13.4.3.2, denoted as IIC-2 DAMPs. The critical role of mtDNA in severe trauma has been outlined in Sect. 8.3.3.3. The involvement of this DAMP in TBI could be demonstrated in investigations on the CSF of pediatric patients [70]. As reported, the mean CSF mtDNA in pediatric TBI was increased in comparison to controls. Remarkably, the CSF mtDNA concentration in pediatric patients who later died or had a severe disability was significantly higher than that of the survivors. Moreover, the authors found a significant correlation between CSF mtDNA and HMGB1, indicating that both DAMPs are increased in the CSF following TBI in pediatric patients.

### 9.2.6.4 S100 Proteins

S100 proteins have been described in Vol. 1 [1], Part IV, Sect. 12.2.4.2, denoted as constitutive IA-1 DAMPs, and Sect. 14.2.2.4, denoted as inducible IIIA-1 DAMPs. Out of the family of S100 proteins, S100 B proteins have been reported as classical serum biomarkers in TBI, first published already in 1995 [71], and now regarded as a critical DAMP. Similar to other DAMP levels such as HMGB1, the protein was found to be increased in the bloodstream in the acute phase of the trauma and assessed as one of the strongest single predictors of unfavorable TBI outcome [72]. Studies in patients with TBI revealed a primary peak of S100B level during the time of the initial injury, followed by a secondary peak resulting from the second injury predicting an unfavorable outcome [73]. In an analysis of serum levels of S100B proteins in pediatric patients with TBI, median serum levels of S100B at admission were shown to decrease significantly 1 week after TBI [74]. Follow-up of these patients revealed that serum S100B levels 1 week after injury in patients with unfavorable 6-month outcomes were significantly higher than levels 1 week after injury in patients with favorable outcomes. The authors concluded that serial measurements of serum S100B may help to assess brain damage and clinical outcome of pediatric patients with TBI.

A role of S100 proteins has also been investigated in white matter damage after TBI. As reviewed [5], acutely elevated serum levels of S100B were associated with
patient mortality and poor acute and chronic outcomes after severe TBI and were predictive of cognitive function at 4 months after pediatric mild TBI.

9.2.6.5 Oxidation-Specific Epitopes
Membrane-bound OSEs (denoted as IIB-1 DAMPs) have been described in Vol. 1 [1], Part IV, Sect. 13.3.2, and briefly resumed in Sect. 3.4.3.2. They include molecules such as PS, OxPLs containing OxCL, PC, or PE headgroups, as well as 4-HNE, MDA, and oxidized phosphatidylethanolamine (OxPE), all of which are sensed by a broad range of cellular and humoral PRMs (compare also Vol. 1 [1], Part IV, Sect. 13.3.2.2. and Fig. 13.1). Of note, in studies of lipid peroxidation in TBI, these OSEs were already detected (reviewed by Bayır’s group in [13]). For example, increased 4-HNE or HNE-modified proteins have been found in brain tissue using various experimental models of TBI, and an increase of MDA was observed in plasma or CSF in patients following severe TBI [75–77].

Intriguingly, first studies provided evidence for a role of OSEs such as oxygenated PE and oxygenated PL in triggering RCD. Thus, as recently reported [78], oxygenated PEs, especially those containing omega-6 fatty acids such as AA and adrenic acid, were shown to trigger ferroptosis, thereby providing a source for emission of large amounts of further DAMPs. By contrast, oxidation of CL to OxCL—also generated in the injured brain [12]—was demonstrated to be a required step in the execution of apoptosis [79, 80]. Indeed, the temporal profile of CL oxidation in the injured brain was found to indicate the initiation of apoptosis 3 h following TBI [81].

In sum, evidence is accumulating that redox signaling in ferroptosis and apoptosis is based on specific engagement of two different classes of phospholipids; however, in TBI, both ferroptosis and apoptosis (when transforming to secondary necrosis) may serve as a source of emission of DAMPs: again an impressive example of a “DAMPs axis” operating in acute organ injury.

9.2.6.6 Concluding Remarks
There is an increasing number of reports on DAMPs in TBI—less in alcohol-related brain injury—which document the growing pathogenetic role of these molecules in acute brain injury. It has become evident—like in all kinds of organ injuries and given the complexity of pathophysiological processes in TBI—that there are various DAMPs released from cells succumbing RN in the traumatically injured brain. Recognized by PRM-bearing cells such as microglial cells, astrocytes, and neurons, they trigger intracerebral life-threatening proinflammatory signaling pathways that may culminate in brain death. Certainly, as potential therapeutic targets, the list of these molecules mentioned here will be supplemented soon.

9.2.7 SAMPs in Brain Injury
To date, only a few studies on the inflammation-resolving function of SAMPs in TBI have been published. As discussed above, at later stages after injury, SAMPs...
such as LXs, Rvs, and Pds reportedly contribute to the resolution of inflammation. In this context, oxidized PtdSer has been discussed as a potential SAMP involved in TBI. However, “To date, no studies have directly connected PS oxidation and coagulation status in TBI, but it is possible that oxidized PS may prevent injury propagation through an unexplored role in promotion of coagulation” [13]. Interestingly, in an investigation of the effect of SPMs on posttraumatic sleep and functional outcome following diffuse TBI in mice, the resolvins AT-D1 and E1 were found to differentially impact the functional outcome, posttraumatic sleep, and microglial activation following diffuse brain injury in the mouse [82].

Of great interest is the role of the SAMP extracellular adenosine in brain injuries. Indeed, TBI is known to be associated with increased brain levels of extracellular adenosine (reviewed in [83]). For example, in studies in pediatric patients with severe TBI, CSF adenosine concentration was observed to be increased in a time- and severity-dependent manner in infants and children after severe head injury [84]. The authors argued that the association between CSF adenosine and glutamate concentrations may reflect an endogenous attempt at neuroprotection against excitotoxicity after severe TBI. In subsequent studies on mice undergoing experimental TBI, this early adenosine release response was shown—via activation of purine A1 receptors—to suppress seizures [85] and microglial response-mediated brain inflammation [86]. Intriguingly, the authors concluded [86] that the activated A1 receptor “is an endogenous inhibitor of the microglial response to TBI, likely via inhibition of proliferation, and this may represent a therapeutic avenue to modulate microglia after TBI”—a recommendation that was echoed by Jackson et al. [83]: “Developing therapeutics that recruit astrocytes to produce/release adenosine could have beneficial effects in TBI” (for purinergic receptors, compare Sect. 2.3.3, and Vol. 1 [1], Part II, Sect. 5.3.4).

Another SAMP, PGE2, was also observed to contribute to the therapeutic efficacy of MSCs in experimental TBI [87]. In this study on mice, among the immunomodulatory factors assessed, the therapeutic benefit of MSCs was observed to correlate with the secretion of PGE2 by MSCs before treatment.

Also of interest in this context is a report on AnxA1 in BBB protection after experimental intracerebral hemorrhage [88]. This study on an experimental intracerebral hemorrhage model in rats provided evidence suggesting that the proresolving effect of AnxA1 may also participate in a protective effect on intracerebral hemorrhage-induced secondary brain injury.

Together, the beneficial function of some SAMPs in TBI has been documented; however, more targeted studies, in particular, with the use of SPMs, are needed to confirm their protective abilities in TBI.

**9.2.8 Résumé**

Although there is a lack of effective treatment for TBI recovery today, the efforts for developing therapeutic strategies on TBI recovery have been continuously made over the past several decades. Besides improvement of standard medical and surgical interventions, attention should also be paid to the use of DAMPs inhibitors and...
administration of SAMPs or their derivates. Indeed, a growing number of reports on DAMPs released from injured cells and tissue during TBI have confirmed their pivotal role in the initiation and regulation of inflammatory responses, which induce the damage cascade leading to secondary brain damage. Nevertheless, future studies are needed to define the role of SAMPs in brain injury. It can be expected that results from such future studies, in particular, with the use of SPMs in brain trauma will provide new TBI treatments by controlling resolution and downstream mechanisms of neuroinflammatory responses.

Also, subroutines of RN emerge as future therapeutic targets for protecting the injured brain. As mentioned above, the occurrence of necroptosis, pyroptosis, and ferroptosis in an animal model of TBI has already been described. Administration of distinct RN inhibitors has to be taken into consideration aimed at preventing a priori emission of DAMPs. For example, in studies on a murine TBI model, application of ferrostatin-1 (a ferroptosis inhibitor, also known as Fer-1) by cerebral ventricular injection was recently demonstrated to significantly reduce neuronal cell death and improve long-term cognitive and motor function [14]. Further studies in this field are now required to determine the therapeutic window of such inhibitors and develop clinically feasible drugs.

9.3  Acute and Chronic Lung Injury

9.3.1  Introductory Remarks

Acute lung injury is an acute inflammatory disorder with substantial morbidity that can develop into a complex pulmonary process first officially described as ARDS in 1967 [89]. This life-threatening—in about 40% of patients lethal—disorder develops in most cases within 2–5 days of hospitalization and is usually diagnosed clinico-radiographically. Of note, if the timely homeostatic resolution of acute lung inflammation is unrestrained, or if exposure to toxic environmental factors turns out to be acute repetitive or persistent, a COPD can develop. Again, this COPD is a life-threatening disorder that is associated with high morbidity and mortality and, thus, creates enormous challenges for healthcare systems. Here, both diseases are examined in more detail in light of the danger/injury model.

9.3.2  Acute Lung Injury → Acute Respiratory Distress Syndrome

As touched, ALI, when proceeding to ARDS, is associated with high mortality and morbidity rates that increase with disease severity (for reviews, see [90–96]). In the earlier periods, there were some difficulties with an accurate assessment of the clinical symptomology of ARDS. Then, in 2012, the Berlin definition was published stressing the mutually exclusive categories of the disease: mild, moderate, and severe—as based on the degree of hypoxemia and four ancillary variables for severe ARDS. These are radiographic severity, respiratory system compliance, positive end-expiratory pressure, and corrected expired volume per minute (these variables
were later removed because they did not contribute to the predictive validity of severe ARDS for mortality) [97].

In light of new insights into mechanisms of controlled and uncontrolled DAMP-promoted efferent innate immune responses, mild ALI-induced pulmonary inflammation (i.e., pneumonia) resulting in resolution of the inflammatory response may reflect a controlled protective innate immune response, whereas ALI→ARDS represents a typical dysregulated overshooting efferent response caused by emission of DAMPs in excess.

### 9.3.3 Regulated Cell Death and Necroinflammation in Acute Lung Injury

Recently, the event of RCD in ARDS has been well appreciated and is of growing particular importance (for subroutines of RCD, see Sect. 4.3 and also Vol. I [1], Part V, Chpt. 19). Besides apoptosis of cells of the distal pulmonary epithelium and the endothelium [98, 99], necroptosis is discussed as another emerging subroutine of RCD. Thus, in experiments on mice, RIP3-mediated necroptosis of alveolar wall EpCs and macrophage-like cells was demonstrated to be a significant mechanism of enhanced inflammation and lung tissue injury in high dose LPS-induced severe ARDS [100] (compare Fig. 9.2). Moreover, in an experimental rat model of ARDS, necroptosis could be

---

**Fig. 9.2** Simplified schematic diagram of a narrative model of the action of DAMPs and SAMPs in acute lung injury. Injury-induced DAMPs (e.g., released from type I alveolar epithelial cells succumbing to RCD) activate innate immune cells such as polymorphonuclear leukocytes and M1-like macrophages that in turn promote acute pulmonary inflammation via secretion of pro-inflammatory mediator substances (e.g., cytokines). SAMPs mainly secreted by injury-activated M2-like macrophages contribute to resolution of alveolar inflammation via promotion of anti-inflammatory mechanisms (e.g., production of IL-10), efferocytosis, and reepithelialization—the end result being repair of the alveolar barrier. *AECI* type I alveolar epithelial cells, *AECII* type II alveolar epithelial cells, *ECM* extracellular matrix, *MO* macrophage, *PMN* polymorphonuclear leukocytes, *RCD* regulated cell death. (Sources: [110–113, 164, 455])
induced by oleic acid, also suggesting that the pathogenesis of this disease may involve necroptosis [101]. These first experimental findings are supported by a clinical study showing that blood transfusion-related ALI enhances the susceptibility to ARDS in critically ill transfused patients and mice through necroptosis of lung ECs [102]. Of note, besides necroptosis of alveolar cells, initial emerging evidence suggested that necroptosis and pyroptosis of alveolar macrophages may also play essential roles in the progression of lung inflammation resulting in ARDS [101, 103]. Nevertheless, the role of necroptosis and pyroptosis (and probably also ferroptosis) in the development of ARDS is to be determined more solidly by further targeted studies.

Importantly, a role of NETs/NETosis in the pathogenesis of ARDS has also been reported. Based on an analysis of bronchial aspirates from ARDS patients showing NETs to be significantly correlated with the degree of ARDS, a hydrochloric acid (HCL) aspiration-induced ALI model was developed in mice to assess whether NETs are pathogenetic and whether targeting NETs is protective [104]. Indeed, with the use of this experimental model, the authors were successful in demonstrating that HCl aspiration causes severe lung injury, together with significantly increased levels of NETs, which are correlated with the severity of ALI → ARDS.

Together, these first observations point to subroutines of RCD as critical sources of DAMPs, which trigger necro-hyperinflammatory responses involved in the pathogenesis of ARDS. Nevertheless, the molecular mechanisms responsible for the development of these ARDS-associated conditions—though increasingly learned—are still not fully understood, but there is growing evidence in support of the notion that the DAMPs play a vital role in these pathologies.

9.3.4 Pathogenesis of Acute Lung Injury → Acute Respiratory Distress Syndrome (in Brief)

9.3.4.1 General Remarks
Development of ALI → ARDS is a classical complication after major trauma with shock, but other numerous acute alveolar injury-causing insults have been described including but not limited to infection, mechanical ventilation, acute bacterial or viral pneumonia, burns, aspiration of gastric contents, immunologically mediated pulmonary hemorrhage, and vasculitis. Predisposing clinical factors that may contribute to that kind of an oversooting innate immune response include acute pancreatitis, blood transfusions, drug overdose reactions, and cigarette smoke or toxic gas inhalation. Moreover, genetic polymorphisms that predispose individuals to the injurious effects of specific bacteria or viruses may also influence the development of ALI and ARDS (for competent papers, see [90, 92, 96, 105, 106]).

9.3.4.2 MAMP/DAMP-Driven Promotion of Lung Inflammation in Acute Lung Injury → Acute Respiratory Distress Syndrome
Despite many years of experimental and clinical studies, the exact molecular mechanisms governing pathogenesis of ALI → ARDS remained unclear until it became evident that MAMP/DAMP-triggered innate immune responses play a crucial role in this peculiar organ injury as well (additional involvement of MAMPs refer to pathogen-mediated ALI).
The typical pathophysiological scenario observed in ALI and ARDS is based on an initial acute pulmonary inflammatory response due to direct or indirect lung injury caused by those factors listed above. The severe uncontrolled inflammatory responses are the result of secretion/release of cytokines (e.g., TNF, IL-1β, IL-6, IL-8) and histamine by MAMP/DAMP- or DAMP-activated pulmonary PRM-bearing cells such as resident alveolar M1-like macrophages, alveolar epithelial, and vascular cells. These cells—in terms of an amplifying inflammatory response and associated with increased vascular permeability—recruit further mobile PRM-expressing cells such as neutrophils, monocytes, macrophages, platelets, and DCs to the lung. Excessive neutrophilic influx into the alveolar space leads to the generation of ROS and further proinflammatory factors, which could aggravate the disruption of the alveolar–capillary barrier (compare Fig. 9.2).

Notably, in the case of pathogen-induced ALI, T and B lymphocyte as cells of the pathogen-specific adaptive immune response join the family of infiltrating cells. Arrived in the lung, the mobile immune cells, in turn, get activated to produce further cytokines and chemokines as well as cytotoxic mediators such as ROS and proteolytic enzymes (proteases) and granular enzymes. Additionally, recruited dying neutrophils produce NETs. These products at the efferent arm of the innate immune response (in case of infection, plus adaptive immune T and B cells) mediate vascular endothelial and alveolar epithelial cell damage that leads to disruption of the alveolar endothelial and epithelial barriers (for in-depth articles, see [90, 95, 107, 108]). It is this alveolar epithelium that can be regarded as a critical target of the innate immune attacks. It is composed of two types of cells, which, under homeostatic conditions, form a natural barrier. Type I cells, which make up 90% of the alveolar epithelium, are sensitive to toxins and oxidative stress and are prone to necrosis. They are easily injured compared to PRM-expressing type II cells, which make up 10% of the alveolar surface area and—as a defender of the alveolus—are involved in surfactant production and sodium transport, as well as induce proliferation and differentiation to type I cells contributing to alveolar epithelial repair [109] (compare Fig. 9.2, and also Vol. 1 [1], Part III, Sect. 9.2.4). The interaction between the epithelial barrier and the other barrier, that is, the microvascular endothelium plays a crucial role in controlling fluid accumulation in the alveolar space. The various inflammatory and cytotoxic mediators mentioned above promote RCD of both alveolar type I and II EpCs and ECs (apoptosis, necroptosis) leading to disruption of the barriers associated with hyperpermeability, resulting in pulmonary edema, intrapulmonary hemorrhage, severely impaired gas exchange, decreased lung compliance, and increased pulmonary arterial pressure. Further, the injury of alveolar epithelium impairs active fluid transport mechanisms in the lung, preventing reabsorption of edema fluid from the alveolar space, which is a key step in the resolution of ALI → ARDS (reviewed in [90, 95, 98, 107, 108]).

9.3.4.3 SAMP-Mediated Protection of Pulmonary Function in Acute Lung Injury

Finally, in those patients with ALI who do not proceed to or survive ARDS, a resolution of inflammation can be observed characterized by fluid clearance and solute reabsorption from the alveolus [110, 111]. Several mechanisms central to
controlling the resolution of lung inflammation and injury have been discussed, including enhanced efferocytosis of apoptotic neutrophils/eosinophils performed by antiinflammatory and/or proresolving macrophages. In particular, a shift from M1-like to M2-like macrophages appears to be the principal mechanism involved in this resolution of inflammation stage (compare Fig. 9.2). The M2-like macrophages promote alveolar epithelial cell transition and fibrosis formation mainly by release of TGF-β and IL-10 [110, 112, 113] (for M1-like and M2-like macrophages, see Sect. 5.3.2.3 and also Vol. 1 [1], Part III, Sects. 8.2.2.2 and 8.2.2.3 and Fig. 8.2).

9.3.4.4 Pathohistological Stages in Acute Lung Injury
The sequelae of the efferent innate immune pathways in ALI are reflected by typical pathohistological stages. The early initial scenario is the exudative stage characterized by diffuse alveolar damage; a subsequent second stage of proliferation is manifested by resolution of pulmonary edema, proliferation of type II alveolar cells, squamous metaplasia, and early deposition of collagen; the third stage of fibrosis is characterized by obliteration of normal lung architecture, diffuse fibrosis, and cyst formation [95, 114, 115]. For patients who survive ARDS, a fourth stage can be distinguished: the resolution stage that usually remains with minimal lung damage [112].

9.3.4.5 Concluding Remarks
There is growing evidence for a critical role of DAMPs in the pathogenesis of both pathogen- and sterile injury-mediated ARDS, its pathophysiologic hallmark being disruption of the alveolar–capillary barrier. As observed in other acute organ injuries, subtypes of RCD have been discovered to serve as a crucial source of DAMP emission. Of equal importance, however, are recent studies showing that SAMPs are involved in the resolution stage of ARDS. The following sections should add some more details to these new pathogenetic perspectives in this life-threatening acute lung disease.

9.3.5 DAMPs in Acute Lung Injury

9.3.5.1 General Remarks: Emission of DAMPs upon Sterile and Infectious Lung Injury
An increasing number of articles are devoted to a pathogenetic role of intrapulmonary DAMPs emission in ALI → ARDS, including sepsis-induced ARDS, among them reviews published by Tolle and Standiford [116] and Englert et al. [117].

Also, a function of DAMPs in (massive) transfusion-related acute lung injury (TRALI) resulting in ARDS has been already discussed [118, 119]. On the other hand, other extrapulmonary sources of DAMPs may also aggravate ALI. For example, in studies on rats, release of mtDNA associated with hip fracture was found to promote lung injury [120]. Here, it should be particularly stressed that DAMPs have also been demonstrated in severe infections associated with ALI → ARDS, an observation that underlines the correctness of the danger/injury model in Immunology, namely, that a robust
pathogen-induced inflammatory defense response is mainly provoked by the emission of DAMPs upon pathogen-mediated tissue injury. When this response is uncontrolled and exaggerated, it can lead to a life-threatening disease such as ARDS. This topic has been thoroughly reviewed by Kang et al. [121] discussing the demonstration of organ-specific DAMPs as involved in pathogen-induced sepsis, often associated with ARDS. For example, remarkably high levels of HMGB1 have been found in the pulmonary epithelial lining fluid of patients with sepsis [122]. Moreover, host-derived DAMPs, such as OxPLs and HMGB1, were shown to be generated during influenza virus infection and causing ALI [123].

Thus, given the growing attention paid to DAMPs as potential therapeutic targets in this life-threatening lung disease, they deserve a few more words.

9.3.5.2 High Mobility Group Box 1

Already before the term DAMPs was coined, in a study in mice, HMGB1 was shown to mediate acute inflammatory lung injury [124]. In this study, HMGB1 given intratracheally was observed to promote an acute inflammatory response to the lungs, with neutrophil influx and accumulation, the development of alveolar edema, and increased pulmonary release of IL-1β, and secretion of TNF. Histological investigation revealed diffuse alveolar damage identical to the pathological findings in ALI → ARDS [124]. In other sets of experiments in rats, intratracheal instillation of HMGB1 was found to provoke persistently exacerbated acute lung inflammation, induction of inducible nitric oxide synthase (iNOS) in alveolar macrophages, and increased lung nitric oxide production [125]. The authors concluded that iNOS expressed by alveolar macrophages facilitates the development of HMGB1-induced ALI.

Interestingly, in a murine hemorrhage model associated with ALI, neutrophils expressing HMGB1 was detected in the lungs after hemorrhage [126]. The intrapulmonary expression of HMGB1 was found to be increased within 4 h of hemorrhage and then remained elevated for more than 72 h after blood loss. The authors argued that these results demonstrate that hemorrhage leads to increased HMGB1 expression in the lungs, primarily through neutrophil sources, and that this IA-1 DAMP participates in hemorrhage-induced ALI.

In more recent studies on an adult mouse model, inhibition of extracellular HMGB1 was shown to mitigate hyperoxia-induced inflammatory ALI [127]. In other lines of studies in rats, inhibition of HMGB1 by the antiinflammatory agent ketamine was demonstrated to alleviate LPS-induced ALI [128]. In a subsequent similar study in rats, inhibition of HMGB1 by paenol (the main active component of Paeonia suffruticosa, which has been used to inhibit the inflammatory response in traditional Chinese medicine), was found to attenuate LPS-induced ALI as well [129].

Again, in other sets of experiments in rodents, blocking of HMGB1 with an anti-HMGB1 antibody was found to mitigate ALI. Thus, in one study on a ventilator-induced lung injury model in rabbits, intratracheal instillation of such an antibody improved oxygenation, limited microvascular permeability and neutrophil influx into the alveolar lumen, as well as decreased concentrations of TNF in
bronchoalveolar lavage fluid [130]. In studies on a murine model of *Pseudomonas aeruginosa* pneumonia, exposure to hyperoxia reportedly led to a significant elevation in concentrations of airway HMGB1 and increased mortality in infected mice [131]. Treatment of these mice with a neutralizing anti-HMGB1 monoclonal antibody resulted in a reduction in bacterial counts, injury, and numbers of neutrophils in the lungs, as well as an increase in leukocyte phagocytic activity compared with mice receiving a control antibody. This improved phagocytic function was observed by the investigators to be associated with reduced concentrations of airway HMGB1 [131].

Intense clinical studies on HMGB1 in patients with ALI → ARDS are still limited, though—according to an early clinical observation already in 1999—high HMGB1 levels were already found to be associated with increased mortality in subjects with severe sepsis [132]. Further, one small study of 21 patients with sepsis-induced ALI revealed that HMGB1 levels were higher in epithelial lung fluid and plasma compared to controls. Interestingly, these findings could be observed persistently during both the acute and subacute phases of ARDS [133]. In subsequent investigations, HMGB1 levels were determined in bronchoalveolar lavage fluid of trauma patients during mechanical ventilation and ventilator-associated pneumonia [134]. The authors reported that long-term mechanical ventilation is associated with increased HMGB1 levels that are elevated during ventilator-associated pneumonia compared with healthy volunteers. In a more recent study on patients with severe pneumonia and ARDS requiring mechanical ventilation [135], the investigators remarkably observed the day 1 HMGB1 concentration to be a critical, independent biomarker for ICU mortality.

**9.3.5.3 Heat Shock Proteins**

The function of HSPs in ALI → ARDS has not been investigated systematically. In a series of experimental studies on the role of HSP72 in lung inflammation, in vitro assays showed that extracellular HSP72 can induce a dose-dependent increase in IL-8 expression and activation of NF-κB in bronchial EpCs [136]. In subsequent in vivo experiments in mice, the investigator group observed that intratracheal installation of HSP72 can induce upregulation of chemokine and TNF levels, and increase neutrophil influx in bronchoalveolar lavage fluid. Further studies on this model using TLR4 mutant mice revealed an essential role of TLR4 in HSP-mediated lung inflammation [136]. In a previously performed clinical analysis, the presence of extracellular HSP72 was reportedly demonstrated in bronchoalveolar lavage fluid and plasma of patients suffering from ALI [137].

**9.3.5.4 Nucleic Acids**

**Mitochondrial DNA**

A pathogenetic role of mtDNA in ALI → ARDS has been reported as well. In one of the first studies, Sun et al. [138] could show that mitochondrial DAMPs including mtDNA, but also mFPs, can essentially trigger endothelial permeability changes as observed in ALI → ARDS (compare Sect. 8.3.3.3). Subsequent studies used several
models to confirm the pathogenetic role of mtDNA in this life-threatening syndrome. Thus, in a model of *Pseudomonas aeruginosa*-induced vascular injury in perfused isolated rat lungs, mtDNA (originating from the mammalian mitochondrial genome) was demonstrated to accumulate in the perfusion medium substantially [139]. In studies on a murine endotoxemia model, several experiments were performed to prove an effect of mtDNA on ALI [140]. In a first series of experiments using this model, mtDNA was found to be released in the plasma following intraperitoneal injection of LPS. In a second series of experiments, intraperitoneal administration of mtDNA was demonstrated to cause apparent ALI and systemic inflammation associated with increased IL-1β and IL-6 levels. Accompanying analyses provided evidence that the LPS-induced mtDNA release occurred in a TLR4-dependent manner, whereas mtDNA-induced ALI and systemic inflammation happened in a TLR9-dependent but TLR4-independent mode [140]. Subsequent studies on a rat model of full-thickness thermal injury produced similar results by demonstrating increased mtDNA plasma concentrations and—as revealed by related experiments—mtDNA administration-caused severe ARDS. The critical pathogenetic role of mtDNA in the development of ALI → ARDS could be documented by another recent study on a rat intratracheal *Pseudomonas aeruginosa* model [141].

Of note, in a clinical study on patients with suspected ventilator-associated pneumonia, higher levels of mtDNA were detected in the bronchoalveolar lavage fluid [142]. In another clinical study conducted by the same group, mtDNA in transfusion products was suggested to contribute to the development of ARDS after multiple transfusions [119], thereby confirming the first proposal of the “work of DAMPs” operating in TRALI [118]. In these clinical investigations, detectable levels of mtDNA were found in packed red blood cells, fresh frozen plasma, and platelets, with the latter two transfusion products containing significant amounts of mtDNA fragments. Also, the investigators observed a linear relationship between the mtDNA given during transfusion and the serum concentration of mtDNA fragments. Even more remarkably, the quantity of mtDNA in serum measured at 24 h after transfusion predicted the occurrence of ARDS. According to the authors’ conclusion, these findings support the idea that mtDNA DAMPs in transfusion products significantly contribute to the incidence of ARDS after massive transfusions.

Interestingly, apart from mtDNA, mitochondrial peptides—via FPR-1 → MAPKs/AKT signaling—were recently shown to activate type II alveolar EpCs to induce pulmonary inflammation, thereby possibly contributing to ARDS [143].

**Histones**

Besides nuclear NAs, nuclear proteins, that is, histones have been identified as DAMPs to contribute to ALI. As outlined in Vol. 1 [1], Part IV, Sect. 12.2.4.4 and reviewed by Silk et al. [103], histones may be released into the extracellular space in three forms: freely, as a DNA-bound nucleosome, or as part of NETs; but all three forms can be detected in serum after significant cellular death caused by various injuries. As reported in patients with an acute history of severe blunt trauma [144], circulating histones increase to toxic levels within 4 h and correlate with the severity of ALI. The high levels were significantly associated with markers of endothelial
damage and coagulation activation. In in vitro systems, used in parallel to the clinical observation, histones were observed to damage ECs, stimulate cytokine release, and promote NET formation and myeloperoxidase release. In murine trauma models, cytokines and markers for endothelial damage and coagulation activation were shown to increase immediately after trauma or histone infusion significantly. Pathological examinations showed that the lungs were the predominantly affected organ with edema, hemorrhage, microvascular thrombosis, and neutrophil congestion [144].

In another clinical study on patients with ARDS, extracellular histone levels in plasma and bronchoalveolar lavage fluid were also found to be excessively increased and associated with ARDS severity and mortality [145]. In ex vivo investigations, the authors could demonstrate that ARDS patients’ bronchoalveolar lavage fluid induces epithelial and endothelial cell damage remarkably and stimulates cytokine production in the supernatant of the model cell line U937 (a human macrophage cell line).

Together, there is increasing experimental and clinical evidence for a critical pathogenetic role of extracellular histones in the development and progression of ARDS.

### 9.3.5.5 S100A Proteins

The role of S100 proteins such as S100A8 and S100A9 in ALI has already been thoroughly reviewed elsewhere [146–148]. The function of these DAMPs—either passively released from necrotic cells or actively secreted by activated immune cells—is mediated via their cognate PRMs TLR4 or RAGE, although other receptors are also implicated in S100A9 function (for additional information also compare Vol. 1 [1], Part IV, Sects. 12.2.4.2, p. 229 and 14.2.2.4, p. 310). Of note, the role of these DAMPs in ALI is ambivalent in that S100A8 operates as a DAMP exerting proinflammatory effects while S100A8/S100A9 and S100A9 slip into a “SAMP-like” function to convey antiinflammatory properties.

Collectively, the involvement of S100A proteins in ALI has been well documented both in experimental and clinical studies. For example, in studies in rats and mice, S100A9 mRNA was shown to be upregulated in lungs undergoing injurious mechanical ventilation [149, 150]. In patients with ARDS, upregulation of neutrophil-derived S100A12 (and its receptor RAGE) expression in lung tissue and bronchoalveolar lavage fluid was reportedly significantly higher when compared with healthy controls [146, 151]. Also, S100A8/A9 protein levels were found to be elevated in the bronchoalveolar lavage fluid of ARDS patients [146].

A proinflammatory function of S100A proteins was described by Chakraborty et al. [147], referring to studies on in vitro cultured alveolar EpCs and an in vivo murine model of lung injury. The authors could demonstrate that S100A8 drives lung inflammation via activation of alveolar EpCs in a TLR4-dependent manner, as documented by release of cytokines and chemokines [147]. Further, in these studies, the investigators demonstrated that inhaled endogenous S100A8 directly induces neutrophil recruitment into the bronchoalveolar lavage fluid. According to the authors’ conclusion, this observation confirms the significance of this DAMP in
inflammation-related neutrophil immigration, knowing that one of the key features of ALI is infiltration of neutrophils into the lungs.

By contrast to the proinflammatory effect of S100A8, an antiinflammatory function of S100A proteins could be demonstrated by Hiroshima et al. in studies in mice [148]. Again in experiments on a murine lung model using S100A protein inhalation, the authors showed critical functional differences of S100A8/A9 and S100A9 that distinguish them from S100A8. Thus, unlike S100A8, S100A9 was found to promote mild neutrophil and lymphocyte influx, possibly mediated in part by increased mast cell degranulation and selective upregulation of some chemokine genes. Moreover, the S100 proteins did not significantly induce proinflammatory mediators, including TNF, IL-1β, or IL-6. Furthermore, compared to the marked increase induced by S100A8, S100A8/A9 or S100A9 did not alter substantially basal IL-10 mRNA over the time course tested. Also, like S100A8, S100A9 and S100A8/A9 were shown to reduce neutrophil influx in ALI provoked by LPS challenge but were somewhat less inhibitory, possibly, because of differential effects on expression of some chemokines.

Together, the studies on S100A proteins published by Chakraborty et al. [147] and Hiroshima et al. [148]—here briefly reviewed—suggest a proinflammatory role of S100A8 and an antiinflammatory protective role of S100A8/A9 or S100A9 in lung injury. Accordingly, in their conclusion, the authors proposed [148], “that their secretion by infiltrating myeloid cells, and induction in macrophages and EpCs by particular agonists, may contribute to normal lung homeostasis and protection against excessive fulminant inflammation” (in this context, also compare Sect. 3.5.6).

9.3.5.6 DAMPs Activating the NLRP3 Inflammasome
There are some reports in the literature suggesting that MAMPs/DAMPs (i.e., IA-2 DAMPs) contribute to ALI → ARDS via activation of the NLRP3 inflammasome, that is, probably via induction of pyroptosis [152, 153]. In support of this concept are, for example, experimental studies demonstrating that eATP is released during injurious mechanical ventilation, thereby contributing to pulmonary inflammation and lung edema [154, 155]; that is, studies that let suggest a role of this DAMPs in the activation of the NLRP3 inflammasome.

Another IA-2 DAMP, uric acid, was also reported to be involved in ALI mediated by the NLRP3 inflammasome [156]. In these studies, local uric acid levels were found to be increased in patients with ALI; in experiments in mice performed in parallel, allopurinol and uricase were documented to attenuate ventilator-induced alveolar barrier dysfunction. Also, this DAMP was demonstrated to accumulate intrapulmonarily in a bleomycin-induced lung injury model and to promote lung inflammation [157]. The investigators also could show that local administration of exogenous uric acid crystals recapitulates lung inflammation.

9.3.5.7 Extracellular Matrix-Derived Proteins
Increased ECM turnover is a characteristic feature of tissue injury in ARDS. DAMPs released from the ECM in the form of proteolytically cleaved fragments (Class IIA
DAMPs) can reportedly contribute to ALI → ARDS (for class IIA DAMPs, see Sect. 3.4.2 and also Vol. 1 [1], Part IV, Sect. 13.2). Such a DAMP is hyaluronan (HA), or fragment of hyaluronan (fHA) that was shown to be associated with organ dysfunction in ARDS (for HA, see Vol. 1 [1], Part IV, Sect. 13.2.3.2). As reviewed by Esposito et al. [158], increased fHA deposition has been demonstrated in the lung tissue of rats with bleomycin-induced lung injury and in humans suffering from ARDS; also, increased HA synthesis has been observed in nonhuman primates with ARDS. Notably, in a clinical study on ARDS patients [158], increasing circulating and alveolar fHA levels were demonstrated to be associated with the severity of ALI. Moreover, the investigators noticed that alveolar fHA was apparently related to respiratory organ dysfunction rather than systemic organ dysfunction, while circulating fHA was found to be related to systemic organ dysfunction. Given these observations, the authors suggested compartmentalized effects of fHA in ARDS. Mechanistically, they discussed the possibility that—besides others—fHA may initiate inflammatory responses via TLRs [158]. In this context, it is worth mentioning another clinical study on ARDS patients providing evidence that some urinary glycosaminoglycans (GAGs), including fHA, can be used as predictive biomarkers in ARDS [159].

9.3.5.8 Concluding Remarks
Collectively, these data reinforce the concept that DAMPs play a pivotal pathogenetic role in the development of infectious and sterile lung inflammation. Their primary homeostatic function is to initiate a protective innate immune defense response as clinically manifested by a mild ALI symptomatology. However, when emitted in excess, they drive an uncontrolled exaggerated inflammatory response culminating in the life-threatening ARDS [121–123]. And, again, it should be stressed that such an exaggerated potentially lethal DAMPs response occurs in defense against infections—initially intended to rescue the host but, tragically, may even kill the patient: in a way, a kind of suicide.

9.3.6 SAMPs in Acute Lung Injury

9.3.6.1 General Remarks
Homeostatic timely resolution of acute lung inflammation is mandatory: if unrestrained, ARDS can develop; if it becomes chronic, then COPD can develop. In the first place, restitution of barrier integrity is of utmost importance to relieve alveolar edema leading to hypoxemia. Thus, lung-specific proresolving events include clearance of edema and transitional matrix, reepithelialization of the airways, and restoration of pulmonary surfactants. It is the task of SAMPs, in particular, SPMs, to execute these events. In fact, as emphasized by Levy and Serhan [160], restitution of barrier integrity, recruitment of monocytoid cells, as well as promotion of M2-like macrophage-mediated clearance of dead cells and tissue debris are all proresolving responses orchestrated by SPMs (compare Fig. 9.2).
9.3.6.2 Specialized Proresolving Mediators

Previous experimental studies have already demonstrated that SPMs such as LXA4 and RvD1 could regulate the alveolar fluid clearance in ARDS to protect the lung function [161–163]. As recently reviewed by Wang et al. [164], further studies have extended evidence in support of the notion that SPMs might enhance the alveolar epithelium repair, inhibit the proinflammatory cytokines, and upregulate the ion channel activity and protein expression in a receptor-dependent manner to increase the alveolar fluid clearance, thereby contributing to ALI → ARDS resolution [164]. Plausibly, these recent findings have been considered to serve as promising agents for the treatment of ARDS.

9.3.6.3 Adenosine–Prostaglandin E2–Annexin A1

Earlier studies had already identified extracellular adenosine as a protective molecule in inflammatory lung conditions, including acute and chronic lung diseases [90, 165, 166]. In more recent in vitro and in vivo experiments on cell lines and mice [167], the authors reevaluated the role of adenosine kinase during ALI (the adenosine kinase inhibits elevated extracellular adenosine levels). They found that adenosine kinase is repressed during inflammation, both in vitro and in vivo. This repression reportedly translates into a protective response during pulmonary inflammation, as observed in animal experiments involving genetic repression of adenosine kinase. Moreover, the investigators could demonstrate in pharmacological studies that the in vivo inhibition of adenosine kinase (associated with elevated adenosine) mitigates tissue injury during pulmonary inflammation. According to the authors’ conclusion, these data show that adenosine kinase is a valuable target for reducing the inflammatory changes associated with lung injury and should be pursued as a therapeutic option [167].

In a systematic review and meta-analysis, a beneficial effect of inhaled prostaglandins in patients with ARDS was explored [168]. The meta-analysis could demonstrate that inhaled prostaglandins improve oxygenation and decrease pulmonary artery pressures and may be associated with adverse events. However, as concluded by the authors, the use of inhaled prostaglandins in ARDS requires further targeted experiments. More targeted studies on the role of PGE2 in ALI → ARDS are still lacking.

Also, in a recent study evaluating the role of AnxA1 in the treatment of acute radiation-induced lung injury, this SAMP was found to reduce the expression of IL-6 and inhibit the release of myeloperoxidase from monocytes and macrophages [169]. The authors argued that this antiinflammatory effect may underscore the mechanism by which AnxA1 in the plasma of patients with this type of lung injury is associated with treatment outcome.

9.3.6.4 Concluding Remarks

As can be seen from the current literature available, the detection and function of SAMPs in ALI → ARDS is still a poorly explored, however, emerging research field. On the other hand, resolution of inflammation in this disease is an appreciated typical feature, documented by many experimental studies, and a failure to resolve
ongoing inflammation is well-known to increase mortality and prolong morbidity in survivors. Thus, in the course of the currently noticed “high season” of this research discipline, relevant reports on this topic can be expected soon.

9.3.7 Acute Repetitive or Persistent Lung Injury → Chronic Obstructive Pulmonary Disease

9.3.7.1 General Remarks
As already touched above, acute repetitive or persistent lung injury can lead to COPD that is a heterogeneous and complex pulmonary disease, causing significant healthcare burdens worldwide. Thus, the incidence of COPD has increased in the past few decades and has become a major public health problem and will remain a challenge for clinicians within the twenty-first century. Worldwide, COPD is in the spotlight, since its high prevalence, morbidity, and mortality create enormous challenges for healthcare systems (reviewed in [170, 171]). The development of COPD is mainly the result of continued exposure to various environmental risk factors, although genetic host factors have a role in determining disease susceptibility and pathogenesis (reviewed in [172, 173]). Among the environmental factors, cigarette smoking is a significant risk factor for COPD, but environmental tobacco smoking also contributes to its development. Occupational exposure to vapor, dust, gas, and fumes, as well as outdoor air pollution, is another important risk factor for disease exacerbation and mortality.

9.3.7.2 Pathogenesis of Chronic Obstructive Pulmonary Disease
(in Brief)
The clinical features of COPD encompass emphysema, chronic bronchitis, obstruction and destruction of the small airways, and enlargement/disorganization of alveoli, that is, loss of alveolar tissue associated with emphysema. Peribronchiolar fibrosis surrounding the small airways contributes to the obstructive pathophysiology in COPD (for reviews, see [171, 174–176]). The chronic inflammatory course of the disease is aggravated by episodes of acute exacerbations.

Characterization of Chronic Nonresolving Airway Inflammation
Typically, chronic nonresolving airway inflammation in COPD is characterized by activation of the innate immune system, involving neutrophils, macrophages, ILCs, and activated DCs, located in the lung tissue and the airway lumen. Also, the adaptive (auto)immune system is activated in COPD, as documented by lung infiltration of Th1, Th17, and B cells, along with a decrease in Tregs in the airways. Moreover, an impact of the lung microbiome on COPD progression and risk of exacerbation has been described. And not to forget are epigenetic modifications that have been reported in patients with COPD to be sometimes linked to disease severity and susceptibility. Together, all these processes result in this typical heterogeneous and complex pulmonary disease (for reviews, see [175–182]). Importantly, as reviewed by Poh et al. [183], COPD can “overlap” with other respiratory diseases, including
bronchiectasis, fibrosis, and obstructive sleep apnea. While COPD alone confers morbidity and mortality, common features with contrasting clinical outcomes can occur in COPD “overlap syndromes,” such as asthma-COPD, bronchiectasis-COPD, and fibrosis-COPD.

Pathogenetic Mechanisms of Environmental Factors in Promoting Action of DAMPs

Environmental factors, as mentioned above, include inhaled toxic/noxious substances such as cigarette smoke, which were shown to cause subroutines of bronchial RCD such as autophagic cell death, necroptosis, parthanatos, and ferroptosis [184–188]. As outlined in Sect. 4.3 and Vol. 1 [1], Part V, Sect. 19.3, these forms of RCD are associated with release of endogenous DAMPs. Usually, these DAMPs trigger inflammasome-independent proinflammatory responses.

In addition, other environmental factors may operate directly as exogenous DAMPs such as inhaled pathogenic air pollutants, including asbestos, crystalline silica, and airborne particulate matter (see Sect. 3.6). This category of IVA-4 DAMPs triggers inflammasome-dependent proinflammatory processes predominantly.

Pathogenetically, DAMP-promoted chronic nonresolving inflammatory, fibrogenic, and adaptive (auto)immune pathways are involved in the development of this heterogeneous and complex pulmonary disease that causes—as already mentioned—significant healthcare burden (morbidity and mortality) worldwide (for DAMP-promoted innate and adaptive immune pathways, see Vol. 1 [1], Part VI, Chpt. 22 and Part VIII, Chpt. 32; for DAMP-promoted self-perpetuating fibrotic pathways, see Sects. 6.4 and 6.5).

9.3.7.3 DAMPs and SAMPS in Chronic Obstructive Pulmonary Disease

There are already reports about the potential pathogenetic role of endogenous DAMPs in COPD (reviewed in [189–191]). Indeed, several clinical studies could demonstrate the presence of DAMPs (e.g., HMGB1, HSPs, S100A proteins, eATP, and GALs) in the serum and extracellular lung fluids, including bronchoalveolar lavage, epithelial lining fluid, and sputum of COPD patients.

First Evidence for Exogenous DAMPs in COPD

Early reports on the contribution of exogenous IVA-4 DAMPs to the pathogenesis of COPD have also been published. Thus, in studies on RAW 264.7 cells (a murine macrophage cell line) and ex vivo lung tissue explants obtained from elastase-induced emphysema animal models, diesel exhaust particles and a cigarette smoking extract were shown to activate the NLRP3 inflammasome [192], known to contribute to proinflammatory and profibrotic processes [193]. These experimental findings are in agreement with (1) epidemiologic studies pointing to a role of air pollutants in the increase in respiratory symptoms and mortality rate in COPD patients [27] and (2) the direct demonstration of inflammasome activation in the lung tissues from patients with COPD at acute exacerbation [194] (for activation of the NLRP3 inflammasome via exogenous DAMPs, e.g., particles, see Sects. 2.2.5.3 9 Solid Organ Injury
and 3.6; also compare Vol. 1 [1], Part II, Sect. 12.2.5.4, Part IV, Sect. 15.2, and Part VI, Sect. 22.4.2.2).

First Evidence for SAMPs in COPD
According to the new view of COPD as a state of nonresolving bronchial inflammation, there is emerging preclinical and clinical evidence suggesting COPD be pathogenetically linked to insufficient levels or activity of SAMPs, in particular, SPMs (reviewed and discussed in [195–197]). Thus, in vitro and preclinical in vivo studies could show that SPMs have bronchoprotective proresolving effects. For example, RvD1 was demonstrated to reduce significantly neutrophilic lung inflammation and proinflammatory cytokine production caused by smoke exposure and promote differentiation of M2-like macrophages associated with enhanced capacity for neutrophil efferocytosis [198]. Also, in this study, RvD1 was found to accelerate the resolution of lung inflammation when given after the final smoke exposure. Clinically, patients suffering from moderate to severe COPD were observed to have reduced levels of LXA4 and LXB4 in exhaled breath condensates [199, 200].

9.3.7.4 Concluding Remarks
Together, these studies again prove the concept of the action of agonist ↔ antagonist, that is, DAMPs ↔ SAMPs in the pathogenesis of diseases, and further highlight essential mechanisms by which DAMPs and SAMPs can positively and negatively influence promotion and resolution of inflammation, thereby contributing pathogenetically to a chronic inflammatory disease, here chronic lung inflammation manifested as COPD. In addition to these insights into lung physiology and disease pathogenesis provided by measuring the presence of DAMPs and SAMPs, monitoring of a DAMP/SAMP signature would be an additional option to improve current therapeutic modalities. This concept would allow us to define and design an appropriate and individualized strategy for the treatment of COPD patients (DAMPs as therapeutic targets and SAMPs as therapeutics; see Sect. 9.9.3), without risking the untoward side effects (i.e., immunosuppression), mediated by traditional antiinflammatory medications.

9.3.8 Résumé
Research work on DAMPs in ALI → ARDS has undoubtedly contributed to understanding its pathogenesis/pathophysiology. In particular, the recognition that DAMPs are emitted during the very treatment aimed to reduce mortality, that is, therapeutic mechanical ventilation, has opened new ways of therapeutic strategies. Additionally, by understanding the role of DAMPs as biomarkers in the pathophysiology of ALI → ARDS, a new category of rational therapeutic targets has gained considerable attention. Moreover, the new mechanistic insights into the process of transition from DAMP-promoted inflammation to SAMP-driven resolution of inflammation are now appreciated as a critical prerequisite to survive the hyperinflammatory and subsequent fibroproliferative stages of ALI → ARDS. Plausibly, in case of progressive
therapy-resistant ALI → ARDS (that might eventually proceed to COPD), administra-
tion of SAMPs would be a stringent therapeutic option to implement soon clin-
ically (see Sect. 9.9.3.3). Certainly, to reach this goal, further targeted studies on 
experimental animal models of ALI are needed. In particular, sophisticated determi-
nation of DAMPs and SAMPs, including monitoring the DAMP/SAMP signature, 
during different phases of ARDS would be necessary to identify those patients in 
whom such a therapeutic intervention could be beneficial. Similar concluding 
remarks can be made for DAMPs involved in COPD. Current studies so far available 
demonstrate that DAMPs occur in both lung microenvironment and serum. 
Nevertheless, further exploration of DAMPs in their capacity to influence COPD 
progression is needed. In particular, that is, in the burning interest of current environ-
mental research and public health, it is time for urgent health studies on the pathoge-
netic role of air pollutants operating as exogenous DAMPs in COPD.

# 9.4 Acute and Chronic Kidney Injury

## 9.4.1 Introductory Remarks

Acute kidney injury is a common life-threatening inflammatory disorder, with 
reported mortality rates up to 50% with the most severe diseases [201–203]. Of 
note, AKI, in case of a failure of inflammation resolution associated with incom-
plete recovery from the acute disorder, can transit to chronic kidney disease (CKD), 
resulting in severe fibrosis clinically manifested by end-stage renal failure. Besides 
AKI, acute repetitive or persistent insults to the renal parenchyma associated with 
chronic inflammation in terms of nonresolving inflammation can also result in per-
manent fibrosis and renal dysfunction, which, if left untreated, may progress to 
CKD. Both diseases are briefly addressed in the following.

## 9.4.2 Acute Kidney Injury → Acute Renal Failure

Acute kidney injury as caused by local and systemic stimuli including ischemia 
reperfusion, nephrotoxic insult, renal hypoperfusion, volume depletion, hypoten-
sion, infection/sepsis, and major surgery is characterized by an abrupt decrease in 
glomerular filtration rate, clinically manifested as a rapid decline of kidney func-
tion. This organ-specific acute injury is further characterized by damage to tubular 
EpCs and ECs and robust inflammatory responses including intrarenal infiltration of 
inflammatory cells (e.g., leukocytes, macrophages), as well as upregulation of che-
mokines and cytokines (reviewed in [204–206]).

Acute renal injury is dangerous and costly, affecting around one in five patients’ 
emergency admissions to the hospital. The organ-specific injury, formerly known as
“acute renal failure (ARF),” has been traditionally described as a rapid decrease (ranging from hours to weeks to less than 3 months) in kidney function as measured by increases in serum creatinine. A variant, acute traumatic AKI, is a serious complication and is usually induced by trauma-associated severe hypotension linked to blood loss leading to renal ischemia/secondary IRI as well as crush injuries and rhabdomyolysis.

Another mostly preventable cause of AKI refers to nephrotoxicity induced by drugs such as calcineurin inhibitors and specific anticancer agents (e.g., cisplatin) reportedly. Although nephrotoxicity is most commonly associated with injury in the tubulointerstitial compartment as either acute tubular necrosis or acute interstitial nephritis [207], a growing body of literature has also highlighted the potential for drug-induced glomerular lesions [208]. Several mechanisms are likely to induce nephrotoxicity, including direct damage to DNA and induction of oxidative stress, mitochondrial dysfunction, as well as apoptotic and necrotic renal cell death, all of which known to lead to an extensive inflammatory response (reviewed in [209, 210]).

Together, AKI carries a high rate of unacceptably, long-term morbidity and mortality. As treatment options, renal replacement therapies such as chronic dialysis and kidney transplantation are available.

9.4.3 Regulated Cell Death and Necroinflammation in Acute Kidney Injury

Typically, ischemic renal damage such as drug-induced nephrotoxicity is characterized by subroutines of RCD such as apoptosis, necroptosis, pyroptosis, ferroptosis, NETosis, and mitochondrial permeability transition (MPT)-driven RN, all serving as critical sources of DAMPs [211–214] (see Box 4.1, and also compare Vol. 1 [1], Part V, Chap. 19). Consequently, the DAMPs activate mobile and sessile innate immune cells, including leukocytes, macrophages, and tubular EpCs and ECs to produce proinflammatory cytokines, chemokines, and other inflammatory mediator substances. These cytokines, partly in terms of inducible DAMPs such as TNF, promote further forms of RCD, which may contribute to intrarenal necroinflammation in terms of an autoamplification loop between cell necrosis and the inflammatory response [215, 216]) (for additional information also compare Vol. 1 [1], Part V, Chpt. 20, p. 467 and Fig. 20.1, p. 469). Repeatedly acute or persistent insults to the renal parenchyma associated with chronic inflammation in terms of nonresolving inflammation can result in permanent fibrosis and renal dysfunction, which, if left untreated, may progress to CKD (see below). Of note, there is growing evidence suggesting that both acute renal necroinflammation and kidney fibrosis reflect the work of DAMPs (for further literature, see [211, 215–223]).
9.4.4 Pathogenesis of Acute Kidney Injury → Acute Renal Failure (in Brief)

9.4.4.1 General Remarks
The pathogenesis of the acute disorder exemplified by ischemic AKI has been thoroughly reviewed [224–226] and is predominantly characterized by severe cytoskeletal changes of innate PRM-bearing resident cells such as EpCs and ECs as well as recruitment of innate PRM-expressing mobile cells including leukocytes and macrophages (Fig. 9.3). As typical for efferent innate immune responses, numerous interactions between these cells have been described (for cells of the innate immune system, also compare Vol. 1 [1], Part III).

Thus, following a reduction in effective kidney perfusion, EpCs are unable to maintain adequate intracellular ATP, and its depletion results in various forms of DAMP-emitting RCD. During an ischemic insult, all segments of the nephron can be affected, but the most commonly injured EpC is the proximal tubular cell. Additionally, the other major EpCs of the nephron involved in the pathophysiology of ischemic AKI are those of the medullary thick ascending limb, located distally. As a typical consequence of hemodynamic disturbances and ischemia-promoted...

---

**Fig. 9.3** Simplified schematic diagram of a model illustrating DAMP-promoted renal necroinflammation that may lead to acute kidney failure. Acute kidney injury, caused by local and systemic injurious stimuli, results in various injury-induced subroutines of RCD providing productive sources for the emission of DAMPs. Intrarenal PRM-bearing cells such as leukocytes, macrophages, tubular EpCs, and ECs, following recognition of DAMPs, trigger pathways leading to necroinflammation. In case of insufficient resolution of inflammation, the processes may result in acute kidney failure. EC endothelial cells, EpCs epithelial cells, HMGB1 high mobility group box 1, MPT-RN mitochondrial permeability transition-driven necrosis, mtDNA mitochondrial DNA, MØ macrophage, NETosis formation of neutrophil extracellular traps (NETs) by neutrophils, PRMs pattern recognition molecules, RCD regulated cell death. (Sources: [204–206, 211–214, 223])
ATP depletion, disruption of the actin cytoskeleton occurs that is associated with the loss of tight junctions and adheren junctions resulting in decline of function and decrease in glomerular filtration rate.

9.4.4.2 DAMP-Driven Promotion of Innate Immune Responses in Acute Kidney Injury

Of note, in parallel, DAMP-activated PRM-bearing epithelial proximal tubular cells produce necroinflammatory cytokines, such as TNF, IL-6, IL-1β, IL-8, and TGF-β, as well as chemokines such as CCL2 and CCL5 [227, 228] (for chemokines, see also Vol. 1 [1], Part VI, Sect. 22.5.11, and Tables 22.1 and 22.2). Inflammation is a critical trigger for further forms of RN (e.g., necroptosis), whereby both events can drive the autoamplification loop of necroinflammation [223]. Mechanistically, cytokines operating as inducible DAMPs may be discussed to trigger secondary RN (e.g., TNF in necroptosis).

Moreover, the PRM-expressing ECs and VSMCs of the microcirculation play critical roles in the pathophysiology of AKI. Thus, ischemia has reportedly profound effects on the renal endothelium, resulting in microvascular dysregulation and continued ischemia and further injury, especially in the outer stripe of the kidney. Importantly, the initial ischemic insult is aggravated by a number of factors, including activation of the clotting cascade, the formation of microthrombi within the vascular lumen, and impaired vascular reactivity. A characteristic feature of the latter is increased vasoconstriction and decreased vasodilatation, promoted by vasoactive mediators including the inducible IIIA-8 DAMP ET-1 [225] (for ET-1, compare Sect. 3.5.3.6, and Vol. 1 [1], Part IV, Sect. 14.2.5.3, and Fig. 14.2). Notably, like DAMP-activated EpCs, DAMP-activated renal ECs also secrete necroinflammatory cytokines that are so important in the pathogenesis of ischemic AKI.

9.4.4.3 SAMP-Promoted Resolution of Inflammation in Acute Kidney Injury

Amazingly, only a few studies have been published regarding the process of resolution of inflammation in AKI. In principle, however, one can assume that the same mechanisms govern this active innate immune process as observed in other models on examining resolving inflammatory pathways. Such an assumption is supported by recent studies showing that polarization of macrophages into the M2-like type contributes to resolution of inflammation in AKI (reviewed in [229], also compare Sect. 5.3.2).

Interestingly, the cold-shock protein Y-box-binding protein-1(YB-1)—a transcriptional and translational factor, which regulates many cellular processes including cell proliferation, DNA repair, and cellular stress response—has recently been reported to orchestrate onset and resolution of renal inflammation via IL-10 gene regulation [230, 231]. However, these preliminary findings suggest that YB-1 is an antiinflammatory molecule rather than an inflammation-resolving factor, i.e., a SAMP. Further publications of exciting data from this research field can be expected.
9.4.4.4 Pathohistopathological Features in Acute Kidney Injury

Histopathologically, these effects are manifested by vascular congestion, edema formation, reduced microvascular blood flow, and margination and adhesion of PRM-bearing innate immune cells to the endothelium, leading to the expansion phase of AKI. Moreover, these AKI-associated vascular changes lead to increased microvascular permeability that is likely to be caused by a combination of factors, including disruption of the endothelial monolayer, alterations in contacts between ECs, and upregulated leukocyte ↔ endothelial interactions (for additional information also compare Vol.1 [1], Part VI, Sect. 22.2.2.2, p. 478, and Fig. 22.2, p. 479). Together, the microvascular function is compromised, leading to DIC and microvascular thrombosis, as well as contributing to decreased local tissue perfusion and organ dysfunction or failure. Expectedly, initial intrarenal DAMP ↔ PRM-triggered, EpC- and EC-secreted chemokines and cytokines—via the phenomenon of leukocyte ↔ endothelial interaction—attract mobile innate PRM-bearing cells such as leukocytes and macrophages to infiltrating the kidney and contributing to amplification of necroinflammation via secretion of further cytokines and chemokines.

9.4.4.5 Concluding Remarks

Together, accumulating evidence suggests that the pathogenesis of AKI is dominated by necroinflammatory pathways triggered by DAMPs derived from various subroutines of RCD (Fig. 9.3). If not stopped at an early stage via inflammation-resolving processes, necroinflammation can lead to ARF or even systemic inflammation and remote organ injury. As with other organ-specific inflammatory processes, renal necroinflammation is the consequence of the emission of DAMPs, which are addressed in the following section.

9.4.5 DAMPs in Acute Kidney Injury

9.4.5.1 General Remarks

There is accumulating evidence in support of the notion that the pathophysiological scenario, as briefly outlined above, is the work of AKI-induced DAMPs. Although, at the time being, research in the role of DAMPs in various causes of AKI is in full swing, not all relevant DAMPs have been fully elucidated so far, whereas most data are available from studies on IRI models. In the following, a few reports about this topic are quoted.

9.4.5.2 High Mobility Group Box 1

The DAMP HMGB1 has been studied in some renal (allograft) IRI models of AKI. For example, in studies on a murine IRI model, HMGB1 was found to be expressed/upregulated, and its blockade was shown to reduce renal IRI by dampening the inflammatory response [232]. In other lines of studies on a murine IRI/AKI model, ischemia alone was found to be associated with release of HMGB1. Subsequent postischemic reperfusion appeared to induce localization of HMGB1 to
renal tubules, peritubular capillaries, and glomeruli, where the renal cells might be more susceptible to ischemic insult [233]. In this study, administration of blocking antibody to HMGB1 was shown to be associated with a reduction in tubular apoptosis and inflammation in situ and in vivo with preservation of renal function. In view of these findings, the authors suggested that released HMGB1 by ischemic renal parenchyma cells may act as an essential early mediator in delayed inflammatory response during IRI, and targeting HMGB1 may represent a potential therapeutic approach in the prevention of clinical IRI associated with kidney transplantation. In support of these findings is a more recently published report showing that preconditioning with recombinant HMGB1 affords significant protection from TLR4-dependent kidney IRI, indicating therapeutic potential [234].

Of note, production of HMGB1 via tubular cells upstream of TLR4 activation was also demonstrated to be promoted by the nephrotoxic calcineurin inhibitor ciclosporin [235]. Moreover, in other lines of studies, neutralizing HMGB1 with an anti-HMGB1 antibody was shown to ameliorate chronic CsA nephrotoxicity via inhibition of the TLR4 signaling pathway [236]. Also, in studies on chemotherapy drugs against cancer, cisplatin-induced poly(ADP-ribose) polymerase activation was found to contribute to HMGB1 release from kidney proximal tubular cells, resulting in the promotion of inflammation during cisplatin nephrotoxicity [237]. However, the research area of DAMPs in drug-induced nephrotoxicity is poorly explored. On the other hand, these molecules may serve as valuable biomarkers in view of the fact that currently used routine biomarkers such as serum creatinine and blood urea nitrogen increase late in the course of injury and only after substantial kidney injury occurs, when the damage may be irreversible. Thus, clinical work is desired to see if DAMPs prove useful in clinical trials with nephrotoxic drugs and can be translated to the clinic for standard patient care (also compare Sect. 9.9.2).

9.4.5.3 S100 Proteins
S100 proteins also belong to the group of DAMPs already studied in models of AKI. For example, in studies on a murine IRI model, S100B was observed to be expressed following postischemic reperfusion of the kidney [232]. In other sets of studies on a renal model of contrast-induced AKI, the S100A8/A9-TLR4-NLRP3 inflammasome pathway was found to be involved in this kind of injury [238]. In a recently reported clinical study on pediatric patients suffering from AKI, S100A8/S100A9 was detected in the urine and proposed by the authors to use as a biomarker for the prediction of adverse outcome of AKI requiring renal replacement therapy [239]. A similar proposal of applying S100A8/S100A9 as a diagnostic and prognostic biomarker in intrinsic AKI was also made elsewhere [240].

9.4.5.4 Mitochondrial DNA
Early pathological changes of mitochondria, including a reduction in abundance, organelle swelling, and fragmentation, have also been observed in the renal tubular epithelium in AKI of different etiologies [241, 242]. Additionally, during renal injury, damaged mitochondria have been reported to release mtDNA [243, 244].
Also, in a clinical study on patients with AKI, mtDNA was measured in the urine, the severity of the disease was quantified, and patients were followed for 90 days [242]. As reported from the authors, the measured urinary mtDNA levels turned out to be a marker of AKI severity, as reflected by its significant correlation with the peak serum creatinine level, duration of hospital stay, and probably the need for temporary dialysis. Again, like other DAMPs, urinary mtDNA has also the potential to serve as a biomarker of AKI.

9.4.5.5 Histones
The role of extracellular histones in AKI has been thoroughly investigated by the Anders group (Allam et al. [245]) (for histones, also compare Vol. 1 [1], Part IV, Sect.12.2.4.4). The authors showed that dying tubular EpCs release histones into the extracellular space that directly interact with TLR2 and TLR4 to induce MyD88, NF-κB, and MAPK signaling. They further demonstrated that these DAMPs also had directly toxic effects on renal ECs and tubular EpCs in vitro. In addition, the investigators could show that direct injection of histones into the renal arteries of mice results in induction of leukocyte recruitment, microvascular vascular leakage, renal inflammation, and structural features of AKI in a TLR2/TLR4-dependent manner. Extended experiments of the group revealed that neutralizing anti-histone IgG can suppress intrarenal inflammation, neutrophil infiltration, and tubular cell necrosis and improve renal excretory function. Notably, in recently extended studies, the Anders group could demonstrate that histones and NETs enhance tubular necrosis and remote organ injury in ischemic AKI [246]. In sum, and also discussed elsewhere [247, 248], the release of histones from dying cells—like other DAMPs described here—support the concept that renal damage-triggered emission of DAMPs elicits a robust efferent innate immune response, which contributes to the pathogenesis of AKI.

9.4.5.6 Uromodulin
Uromodulin is a kidney-specific extracellular inducible DAMP and has been denoted as a IIIA-4 DAMP in this book (for additional information see Vol. 1 [1], Part IV, Sect. 14.2.5.4, p. 318). Uromodulin is selectively produced by the cells of the thick ascending limb and secreted into urine from the apical cell membrane. The function of uromodulin remains elusive, but the available data suggest that this protein might regulate salt transport, protect against urinary tract infection and kidney stones, and have roles in kidney injury and innate immunity (reviewed in [249]). As outlined by Anders and Schaefer [250], under homeostatic conditions, uromodulin is immunologically inert inside the tubular lumen. However, injury to tubular cells enables uromodulin to leak into the interstitial compartment, where it turns into a DAMP that activates interstitial TLR4-bearing DCs [251]. Notably, other lines of studies have demonstrated that uromodulin can trigger activation of the NLRP3 inflammasome resulting in the release of IL-1β [252]. This inducible DAMP has gained increasing attention and recently been proposed to serve as a biomarker in the urinary tract [253].
9.4.5.7 DAMPs Activating the NLRP3 Inflammasome: Crystals
The list of DAMPs involved in AKI has recently been extended by the description of crystals. For example, as outlined [254], the glomerular ultrafiltrate can be enriched with minerals, proteins, or drug metabolites, especially in states of volume depletion promoting supersaturation. This acute condition can induce a sudden onset of crystal formation, resulting in acute episodes of crystal-induced tubular cell injury, interstitial inflammation, and impairment of renal function. Supersaturation of urine leads to crystallization of solutes in renal tubules. Subsequently, these crystallized deposits contribute to kidney injury by inducing direct and indirect cytotoxicity as well as by setting up an autoamplification loop of necroinflammation. Whereas direct cytotoxicity is associated with emission of various DAMPs, indirect cytotoxicity can be mediated via crystal-induced activation of the NLRP3 inflammasome resulting in pyroptosis [255] (for crystals as DAMPs, NLRP3, and pyroptosis, compare also Vol. 1 [1], Part IV, Sect. 12.2.5, and Part V, Sect. 19.3.4).

9.4.5.8 Concluding Remarks
Together, the pathogenetic role of DAMPs in AKI is well-established. So, it is worth to recall the local demonstration of DAMPs in infections again, contributing to a robust pathogen-induced inflammatory defense response to infectious damage [121]. When this response is uncontrolled and exaggerated, for example, in infectious sepsis-induced AKI, it might lead to that feared abrupt decline of kidney function (compare Fig. 9.3).

Consequently, in a first clinical trial on sepsis patients, removal of circulating DAMPs (mtDNA, nDNA, HSP70, HMGB1) during continuous veno-venous hemofiltration therapy was attempted aimed at monitoring the outcome in the patients [256]. Interestingly, the investigators could demonstrate a partial beneficial effect of this therapeutic maneuver by observing a reduction of urinary DAMPs and removal of plasma DAMPs. However, the higher clearance rate of DAMPs, especially HSP70 and HMGB1, was significantly associated with immune disorders (immunosuppression!) and poor prognosis. The unsatisfactory outcome of the study is difficult to explain. At least it may be a warning sign not to interfere therapeutically with DAMP concentrations without strict monitoring of the homeostatic DAMP/SAMP ratio (compare Sect. 7.3.3).

9.4.6 SAMPs in Acute Kidney Injury
The principle of involvement of SAMPs in resolution of inflammation appears to apply for AKI as well though reports on this topic have been published only sporadically. Nevertheless, in various AKI models, including IRI and drug-induced nephrotoxicity, AnxA1, or an AnxA1 mimetic was shown to possess protective properties against renal injury [257–259]. In other lines of studies in mice [260], microsomal prostaglandin E2 synthase-1 (mPGES-1)—an inducible enzyme that converts prostaglandin H2 to PGE2—was observed to exert potentially protective effect against
renal fibrosis and inflammation induced by unilateral ureteral obstruction. Also, as revealed by studies on various AKI models, there is accumulating direct and indirect evidence for a protective role of extracellular adenosine in renal injury-induced inflammation and fibrosis. The topic has been thoroughly reviewed by Bauerle et al. [261]. The authors concluded: “Extracellular adenosine is a central signaling molecule involved in modulation of inflammatory events and mediating adaptation to hypoxia. Adenosine signaling helps alleviate ischemic injury in other organs, and more recently, experimental studies show promising results in AKI as well. Such studies highlight pharmacologic strategies to enhance extracellular adenosine signaling or the targeting of individual adenosine receptors, particularly, the A1, A2A, or A2BAR are effective in preventing or treating AKI from ischemia in murine models.”

Together, there is an emerging role of SAMPs such as AnxA1, PGE2, and extracellular adenosine in promoting resolving inflammatory pathways in AKI, thereby potentially preventing renal fibrosis. Thus, one can expect further progress in this research field when SPMs have been investigated as well.

9.4.7 Acute Repetitive or Chronic Kidney Injury → Chronic Kidney Disease

9.4.7.1 General Remarks

Of note, acute renal injury can transit to CKD in case of incomplete recovery from AKI, leading to long-term functional deficits that are severe and progressive in subpopulations of patients with pre-existing CKD. Indeed, the kidneys from patients recovering from AKI were shown to exhibit chronic dysfunction, tubule atrophy, and interstitial fibrosis [262]. Besides AKI, acute repetitive or persistent insults to the renal parenchyma associated with chronic inflammation in terms of nonresolving inflammation can result in permanent fibrosis and renal dysfunction, which, if left untreated, may progress to CKD. Chronic kidney disease is defined by structural abnormalities or impaired excretory renal function, suggestive of a loss of functional nephrons. Risk factors for the development and progression of CKD include low nephron number at birth, nephron loss due to increasing age, and—as addressed here—acute or chronic kidney injuries caused by toxic exposures or diseases, for example, hypertension, obesity, and T2DM (for review, see [263]).

9.4.7.2 Pathogenesis of Chronic Kidney Disease: Renal Fibrosis (in Brief)

Renal fibrosis, irrespective of its etiology, is a final common stage of almost all CKDs chronic kidney diseases. The progression of CKD associated with chronic inflammation in terms of nonresolving inflammation is characterized by the constant loss of renal cells and their replacement by overshooting repairing responses. Thus, one of the consequences of CKD is glomerulosclerosis and tubulointerstitial fibrosis caused by an imbalance between excessive synthesis and reduced breakdown of the ECM [263, 264]. Typically, as with fibrosis in other organs, renal
interstitial fibrosis results from activation and proliferation of fibroblasts to myofibroblasts, secretion and accumulation of ECM, and displacement of normal renal tubules. Profibrotic factors such as DAMPs are released/secreted by injured tubular epithelial and infiltrated inflammatory cells such as macrophages to promote complex cascades of signaling events leading to this myofibroblastic activation, proliferation, and ECM production [265–267] (see Sects. 6.4 and 6.5; for additional information see also Vol. 1 [1], Part VIII, Sect. 36.4, p. 851).

Notably, the scenario of fibrogenesis is much more complex, and current notions about the fibrotic pathways as described in detail in Chap. 6 include the process of mechanosensing → mechanotransduction mediated by integrins-driven bidirectional “inside-out and outside-in” transmembrane signaling (Sect. 6.3.2, Fig. 6.1); the role of focal adhesions as the key hub for ECM ↔ cell interaction (Sect. 6.3.3, Fig. 6.1); as well as mechanisms of cytoskeleton-driven and nuclear mechanotransduction (Sects. 6.3.4 and 6.3.5, Fig. 6.1).

9.4.7.3 DAMPs and SAMPs in Kidney Fibrosis
Of note, there is growing evidence suggesting that not only acute renal necroinflammation but also kidney fibrosis reflect the work of DAMPs (compare again [211, 215–220, 222, 223]; for fibrosis, see Chap. 6 and Vol. 1 [1], Part VIII, Sect. 36.4). As outlined and argued in Sect. 6.4, fibrosis can be considered a DAMP-driven self-perpetuating process: once myofibroblasts are developed, they take the lead in fibrogenesis via a disastrous ECM/TGF-β-related self-activation process driven by positive feed-forward loops (compare Fig. 6.2).

DAMPs Promoting Renal Fibrosis
As outlined in Sect. 6.4.2, several DAMPs such as HMGB1, S100A8, S100A9, and GAL-3, as well as, in particular, TGF-β (denoted as an inducible DAMP in this book) have been reported to drive fibrogenesis. First direct or indirect evidence for the role of DAMPs in CKD-associated renal fibrosis has already been published. For example, in studies on a murine IRI model, an inhibitor of HMGB1 release, the grape seed proanthocyanidin extract was shown to attenuate IRI-induced chronic renal fibrosis [268]. In other lines of studies on a model of immune-mediated EMT established in human proximal tubular EpCs, human recombinant HMGB1 treatment was shown to induce alterations in epithelial morphology consistent with EMT, thereby indicating a potentially crucial DAMP in the development of renal fibrosis [269]. Again in other sets of studies on a murine model of unilateral ureteral obstruction-mediated renal fibrosis under ER stress, indirect evidence was provided showing that HMGB1 is implicated in the pathogenesis of renal fibrosis [270]. Interestingly, in studies on the same murine fibrosis model, S100A8/A9 DAMPs were demonstrated to promote renal fibrosis in obstructive nephropathy [271].

Importantly, inflammasomes (e.g., the NLRP3 and AIM2 inflammasome) have been shown to be implicated in CKD (reviewed in [272]) indicating that, besides the DAMPs mentioned, other DAMPs that indirectly activate the NLRP3 inflammasome (Subclass IA-2 DAMPs) may be pathogenetically involved in renal
fibrogenesis, found in many chronic renal disorders. As such DAMPs, crystals such as calcium oxalates have already been demonstrated to contribute to renal inflammation in nephrocalcinosis, leading to renal fibrosis (see Mulay and Anders [273]). Interestingly, there is evidence for a pathogenetic role of ASC specks in this scenario, that is, an inducible DAMP as denoted from the perspective of this book (see Sects. 2.2.5.4 and 3.5.4.2). For instance, in studies on the murine unilateral ureteral obstruction model of CKD, ASC speck deficiency was found to significantly reduce inflammatory cell infiltration and cytokine expression and improve subsequent renal fibrosis [274]. Also, in these studies, ASC was observed to be specifically upregulated in collecting duct EpCs. In this context, it is worthwhile mentioning an experiment showing that macrophage uptake of necrotic cell DNA activates the AIM2 inflammasome to regulate a proinflammatory phenotype in CKD [275] (for AIM2 inflammasome, see Sect. 2.2.8).

SAMPs Mitigating Kidney Fibrosis
Also, again, one may discuss the unproven possibility that the process of nonresolving inflammation proceeding to renal fibrosis is pathogenetically linked to insufficient levels or activity of SAMPs. Indeed, initial evidence in support of such a concept has already been published, for example, by Higashi et al. [265] who reported on analysis studies on gene expression patterns among fibroblast populations at different stages of injury or repair. The investigators could demonstrate that inherent gene expression changes in activated fibroblasts accompany the transition from AKI to repair and regeneration. However, in chronic models, activated fibroblasts were found to be resistant to the antifibrotic effects of the SAMP PGE2 due to suppression of a subset of PGE receptors. Also, there is preliminary evidence for the SAMP AnxA1 to have protective effects in renal fibrosis. For instance, in studies on a rat fibrosis model, activation of AnxA1 signaling in renal fibroblasts was demonstrated to exert antifibrotic effects [276].

In other studies on rats with CKD, microRNA-206 overexpression was observed to inhibit EMT of renal tubular EpCs and glomerulosclerosis by inactivating the JAK/STAT signaling pathway via downregulation of AnxA1 [277].

9.4.7.4 Concluding Remarks
Collectively, there is an emerging role of DAMPs and SAMPs involved in acute or chronic injury-promoted kidney fibrosis: a development that raises the pathogenetic mechanisms traditionally known in CKD to another level of complexity. Whereas the impact of DAMPs in renal fibrosis appears to be well-established, the role of SAMPs is still elusive. Thus, harnessing DAMPs as therapeutic targets in renal fibrosis is promising. On the other hand, also under consideration of the emerging role of SAMPs in the pathogenesis of AKI as mentioned above, similar studies to use SAMPs as therapeutics in fibrosis are urgently needed. The justification of this endeavor will be to see if such therapeutic approaches are of any benefit for patients with progressive CKD (compare also below the section on the use of DAMPs as future therapeutic targets and SAMPs as future therapeutics).
9.4.8 Résumé

Today, the pathogenetic role of DAMPs in AKI and CKD is well-established, whereas the contribution of SAMPs to their pathogenesis can be assumed but needs further studies to come to a final assessment and conclusion. Nevertheless, the exact molecular mechanisms for the development of AKI and renal fibrosis have not been fully explored. Notably, recent advances in epigenetic research have also raised interest in the role of epigenetic modifications in acute renal inflammation and fibrosis. In fact, there is already first evidence of activation of epigenetic regulatory mechanisms in both acute renal disease and susceptibility to CKD [266, 278–281]. Should the concept of DAMP-promoted epigenetic modifications once been confirmed, novel therapeutic modalities for AKI and CKD may be provided (compare here also Sect. 6.6; for additional information see Vol.1 [1], Part VI, Sect. 24.2.4.4, p. 644: DAMP-Induced Trained Immunity, as also briefly described in Sect. 3.7). Such a therapeutic approach is even more desirable regarding the potential AKI-to-CKD transition or the acute repetitive/persistent injury-mediated kidney fibrosis mentioned above. Here, the proposal for future continuous monitoring of a DAMP/SAMP signature may help make therapeutic decisions on when to use DAMPs as therapeutic targets and SAMPs as therapeutics.

9.5 Acute and Chronic Liver Injury

9.5.1 Introductory Remarks

Acute liver injury may lead to acute liver failure (ALF), which is an uncommon but severe disease. With an incidence of fewer than ten cases per million persons per year in the developed world, ALF is seen most often in previously healthy adults in their 30s and presents unique challenges in clinical management [282–284]. Acute liver failure can proceed to chronic hepatic failure called “acute-on-chronic liver failure” (ACLF) [285, 286]. On the other hand, acute repetitive or persistent hepatic injuries such as excessive alcohol consumption or viral hepatitis can result in various chronic liver diseases, histopathologically characterized by hepatic fibrosis that proceeds to cirrhosis [287]. These various injury-promoted diseases are briefly addressed here in light of the danger/injury hypothesis.

9.5.2 Acute Liver Injury → Acute Liver Failure

Acute liver injury → ALF is defined as a clinical syndrome characterized by significant liver dysfunction, coagulopathy, and hepatic encephalopathy. The definition includes the fact that it occurs in a patient without pre-existing liver disease and duration of illness in a limited period of time (in about 8 weeks or less). Notably, earlier stages of acute liver injury are usually diagnosed by hepatic dysfunction and
significant coagulopathy (reduced clotting factors) and edema (low albumin), while discernible encephalopathy is still lacking. The etiology varies with geography. Apart from traumatic liver injury, hepatotropic viruses are the most common cause of ALF in developing countries, whereas hepatotoxic drugs are the most common cause of ALF in the western industrialized nations [288].

Acetaminophen (APAP) (also known as paracetamol) hepatotoxicity is a global issue. The intoxication is responsible for nearly half of the ALF cases in the USA and remains the leading cause of liver transplantation. According to information provided by the American National Poison Data System (NPDS), paracetamol is one of the 25 drugs associated with the largest number of pathological fatalities, either alone or in combination with other agents [289].

The mortality of ALF is high and the cause of death is often sepsis/SIRS with MOF. However, timely liver transplantation may save the life of patients. As said, acute liver injury → liver failure is most frequently caused by severe viral infections and hepatotoxic drugs but can also result from prolonged periods of trauma-associated shock followed by hepatic IRI. Accordingly, the proper management of hepatic trauma by clinicians—may it be nonoperative or require hepatic resection in severe cases—should always include the mandatory option of treating hepatic IRI (for further readings, see [283, 284, 290–294]).

9.5.3 Regulated Cell Death and Necroinflammation in Acute Liver Injury

Acute liver injury → ALF is characterized by massive hepatocyte necrosis associated with extensive loss of parenchyma. Today, there is accumulating evidence indicating that hepatocytes succumb mainly from various subroutines of insult-induced RCD, which serve as productive sources of DAMPs emission to trigger hepatic necroinflammatory pathways. Indeed, the hepatocytes can be regarded as the targets of any injury since they have been shown to succumb from apoptosis, necroptosis, ferroptosis, and pyroptosis [295–299].

The various forms of RCD have been best investigated in drug-induced hepatic cell death (reviewed by Iorga et al. [300, 301]). Interestingly, it is not APAP itself that causes hepatotoxicity but rather a reactive metabolite, the \( \text{N-acetyl-p-benzoquinone imine} \) (NAPQI). Under normal circumstances, NAPQI is rapidly converted to nontoxic metabolites by GSH. However, in situations of GSH depletion, such as APAP overdose, chronic alcohol ingestion, and malnutrition, NAPQI persists and leads to liver injury that induces severe liver cell damage and results in inflammation and hepatocyte cell death. Mechanistically, several damaging effects of NAPQI are discussed, including formation of protein adducts by reacting with sulfhydryl groups resulting in mitochondrial dysfunction and cell death (for further reading, see the relevant articles [300, 302–304]).

Notably, there is already first evidence for a role of subroutines of RN in APAP hepatotoxicity, including necroptosis, ferroptosis, and pyroptosis [304–307]. As a
possible vital injurious factor, excessive ROS-mediated oxidative stress has been identified to occur during APAP hepatotoxicity resulting in cell necrosis \cite{308}. This observation let suggest that, besides necroptosis, ferroptotic cell death may also occur in APAP hepatotoxicity (for ferroptosis, see Sect. 4.3.4, and compare Vol. 1 \cite{1}, Part V, Sect. 19.3.3). Indeed, and remarkably, in earlier studies, this subroutine of RCD has already been described to be involved in APAP-induced cell death \cite{309}. Together, the description of the various subroutines of RN in APAP hepatotoxicity strongly suggests a dominating role of DAMPs in mediating innate immune local and lethal systemic necroinflammation in APAP-induced hepatotoxicity.

9.5.4 Pathogenesis of Acute Liver Injury \rightarrow Acute Liver Failure (in Brief)

9.5.4.1 General Remarks
As observed in other acute organ injuries, the various liver insults result in DAMP-promoted necroinflammatory pathways in PRM-bearing hepatic cells, which mount the typical inflammatory milieu via secretion of the inflammatory mediators (including cytokines such as TNF and IL-1\(\beta\), denoted as inducible DAMPs in this book).

In this proinflammatory scenario, the dominating innate immune cells are the Kupffer cells that serve as sentinels for liver homeostasis. Indeed, Kupffer cells, the most abundant tissue resident macrophage population, are key for the maintenance of liver integrity and its restoration after infectious or sterile injury, as well as the local initiation and resolution of innate and adaptive immunity \cite{297, 310}. Notably, the mechanism of resolution of hepatic inflammation is poorly investigated. Nevertheless, in case of insufficient inflammation-resolving processes, acute liver injury can proceed to ALF.

9.5.4.2 DAMP-Governed Innate Immune Responses in Acute Liver Failure
According to current notions, the pathological changes in ALF are the result of innate immune-mediated pathophysiological processes, whereby MAMP/DAMP-governed pathways predominate in ALF caused by hepatotropic viruses, and DAMP-triggered responses are more critical in toxic etiologies.

Regarding pathological features, hepatocyte necrosis occurs due to ATP depletion causing cellular swelling and cell membrane disruption. Although not specifically quantitatively defined, severe liver injury patterns are identified as diffuse, massive, and zonal with massive hepatic necrosis, with near-complete parenchymal necrosis associated with variable inflammation and ductular reaction as the most severe pathologic presentation of ALF \cite{284, 311}. The systemic pathology of ALF at autopsy is generally that of multiorgan system failure. All organ systems can be affected, but most clinically relevant is the development of encephalopathy. Moreover, hemorrhagic complications related to coagulopathy and possible ensuing DIC are common.
9.5.4.3 SAMP-Promoted Resolution of Inflammation in Acute Liver Injury

Interestingly, as reviewed [312], following the acute proinflammatory stage, cytokines and chemokines secreted by activated Kupffer cells further attract the homing and transmigration of protective neutrophils and macrophages to facilitate hepatic inflammation resolution, regeneration, and repair. In more recent studies on an APAP-induced liver injury model in support of this concept, improvement of resolution and liver regeneration was found to be mainly mediated by M2-like macrophages. Mechanistically, the investigators [312] could show that the chemokine CCL5 can facilitate M1-like macrophage polarization and impede M2-like polarization. Similar observations were made in studies on another experimental model of acute hepatic injury in mice, suggesting that polarization of macrophages from the M1-like phenotype to the M2-like phenotype is implicated in amelioration of liver injury and accelerated hepatic regeneration [313]. So far, however, there are only a few reports on the demonstration of SAMPs in acute liver injury, as briefly touched below.

9.5.4.4 Concluding Remarks

Acute liver injury has been observed to mediate remote organ damage, such as brain injury. The pathophysiology of cerebral edema and hepatic encephalopathy, as seen in acute liver injury → ALF, is multifactorial and includes altered BBB secondary to inflammatory mediators leading to microglial activation, accumulation of glutamine secondary to ammonia crossing the BBB, and subsequent oxidative stress leading to depletion of ATP and GTP. These pathogenetic changes ultimately lead to astrocyte swelling and cerebral edema (also compare [314]).

9.5.5 DAMPs in Acute Liver Injury

9.5.5.1 General Remarks

As in AKI, there is increasing evidence for a pathogenetic role of DAMPs in acute liver injury, including drug-triggered hepatotoxicity, which are also supposed to mediate systemic complications. According to studies on liver IRI models and drug-triggered hepatotoxicity, subroutines of hepatic RCD may serve as sources of DAMPs, the subroutines including apoptosis and RN, with recently reported evidence for necroptosis, ferroptosis, pyroptosis, and NETosis [300, 301, 315–320] (for RCD, again compare Sect. 4.3, and Vol. 1 [1], Part V, Chap. 19). Those DAMPs subsequently activate PRM-bearing Kupffer cells. In turn, activated Kupffer cells promote hepatic necroinflammatory pathways via release of cytokines and chemokines that recruit further inflammation-promoting neutrophils and monocytes. Additionally, the DAMPs activate HSCs as the key drivers of hepatic fibrosis (for reviews, see [302, 321–323]). Here, some DAMPs shown to be involved in acute hepatic injury are briefly touched.
9.5.5.2 High Mobility Group Box 1

The participation of HMGB1 in the pathogenesis of acute liver injury has recently been reviewed by Yang et al. [324]. Earlier studies on a murine IRI already demonstrated HMGB1 to act as an early mediator of injury and inflammation in liver IRI, implicating TLR4 as one of the receptors that is involved in the process [325]. A subsequent experiment on a liver IRI model did not only confirm these findings but could also show that HMGB1 (and also histones (see below)) promote NET formation through the TLR signaling pathway. Development of NETs subsequently exacerbates organ damage and initiates inflammatory responses during liver IRI [326]. First clinical studies confirmed these experimental findings by demonstrating increased HMGB1 levels in sera from ALF patients, which correlated with the associated SIRS symptomatology [327].

Also, there is convincing experimental evidence indicating that HMGB1 significantly contributes to drug hepatotoxicity at both the early inflammatory phase and the late regeneration phase [328]. For example, in a lethal APAP overdose model in mice, HMGB1 was found to impair hepatocyte regeneration markedly, and blockade of HMGB1 was observed to enhance the late-phase liver structure recovery significantly [329]. In other experiments on a murine APAP-induced acute liver injury model, neutralization of HMGB1 with a chimeric antibody was shown to attenuate the early phase of post-injury inflammation [330]. Also, in other lines of experiments on APAP-challenged hepatocytes in vivo and in vitro [331], release of HMGB1 was significantly detected in both liver perfusate from APAP-treated mice and culture supernatant of APAP-challenged hepatocytes.

Excitingly, HMGB1 is reportedly also involved in clinical APAP hepatotoxicity. In fact, acetaminophen intoxication is currently known to be one of the best characterized HMGB1-dependent clinical condition in patients. Remarkably, hepatocytes contain more HMGB1 than most other cell types, and hepatocyte-specific conditional hepatocyte-specific HMGB1 knockout has established the crucial role of HMGB1 in drug-induced liver injury but also other liver diseases [332, 333].

For example, HMGB1 was demonstrated to be elevated in the sera of APAP overdose patients with liver injury compared to overdose patients without liver injury [334]. Interestingly, the investigators observed that this DAMP correlated with alanine aminotransferase activity and the prothrombin time. Further, increased total and acetylated HMGB1 was found to be associated with worse prognosis or observed in patients that died or required a liver transplant, compared to spontaneous survivors. The authors concluded from their data that acetylated HMGB1 is a better predictor of outcome than the other markers of cell death.

Consequently, given all this information from targeted studies, HMGB1 has been proposed to be a promising therapeutic target for acute liver injury → liver failure [335].

9.5.5.3 Histones and Extracellular DNA

The role of histones in acute liver injury has been reviewed by Silk et al. [247] and Yang et al. [324]. In experiments on mice, circulating histones (i.e., H3) were found
to exacerbate inflammation with ALF; on the other hand, blockade of these DAMPs with an anti-H3 antibody showed potent protective effects as reflected by reduction in the risk of mortality, suggesting a potential therapeutic strategy for ALF \[336, 337\]. Moreover, in studies on a hepatic IRI model, histones were observed to activate the NLRP3 inflammasome in Kupffer cells through binding to TLR9 \[338\].

Clinically, and in agreement with experimental data, circulating histones have been detected in patients with ALF, demonstrating that these DAMPs operate as critical mediators of systemic inflammation and cellular damage in this human liver disease \[339\]. Notably, these data could be confirmed by a more recent study on ICU patients with acute liver injury showing that the levels of extracellular histones were significantly and independently associated with the presence of acute injury \[340\]. The authors argued that increased histones may contribute to the development of this organ injury in ICU patients, although many other mechanisms may also play crucial roles in its development.

Of note, there is also first experimental evidence for a role of histones in APAP-induced hepatotoxicity. Thus, in a murine model of APAP-induced hepatotoxicity, blockade of histones was shown to attenuate acute fatal liver injury, suggesting that extracellular histones are the major mediators of death in acute fatal liver injury \[337\].

Excitingly, first evidence was provided to suggest also a contribution of extracellular DNA to APAP-induced liver injury. Thus, in clinical studies—accompanied by parallel studies in mice—nDNA fragments and mtDNA were shown to be released into the plasma of patients and mice after APAP overdose \[341\]. The authors discussed that “in patients, the release of DAMPs, such as nuclear DNA fragments and mtDNA during the injury phase, contributes to activation of innate immune cells, which are involved in the removal of necrotic cell debris and thus contribute to the recovery as observed in mice.” The authors concluded that their findings provide strong support for the hypothesis “that mitochondrial dysfunction and DNA damage are critical events in the mechanism of cell necrosis after APAP overdose in patients.” Subsequent experiments in mice confirmed this conclusion by demonstrating that treatment with APAP is associated with DNA release into the hepatocyte cytoplasm, which occurred in parallel with cell death in vitro \[342\].

9.5.5.4 Uric Acid and Extracellular ATP

DAMPs indirectly activating the NLRP3 inflammasome (Subclass IA-2DAMPs) such as uric acid (i.e., monosodium urate [MSU] crystals) and eATP have been identified to mediate APAP-induced hepatotoxicity as well (for IA-2DAMPs and NLRP3 inflammasome, see Sect. \textit{2.2.5.3} and Vol. 1 \cite{1}, Part IV, Sect. 12.2.5, and Part VI, Sect. 22.4.2.2). In earlier studies on an APAP-induced liver injury model, uric acid was already suggested to trigger a cell death-induced inflammatory response \[343\]. Information about eATP as a critical DAMP involved in APAP hepatotoxicity was documented in experiments on mice genetically deficient in the purinoreceptor P2X7. These studies demonstrated that exposure to this DAMP (and nicotinamide adenine dinucleotide), as well as the P2X7 receptor, is required for manifestations of APAP-induced hepatotoxicity \[344\] (for P2X7 receptor, see Sect. \textit{2.3.3} and Vol. 1 \cite{1}, Part II, Sect. 5.3.4.3); for the mechanism of NLRP3...
inflammasome activation via eATP ↔ P2X7 receptor binding, compare Fig. 2.1 and Vol. I [1], Part VI, Fig. 22.11). Other sets of experiments on a murine model of APAP poisoning revealed remarkable changes in the liver environment during APAP overdose that were dependent on eATP signaling [345]. Consequently, inhibition of ATP action was shown to reduce the liver damage significantly. Moreover, in these studies, primary mouse hepatocytes also developed hyperresponsiveness to eATP following APAP exposure, which was prevented by a P2 purine receptor blocker. Also, human-derived cells cultivated in vitro were shown to be protected from these toxic effects when the same blockage strategy was employed. The authors of this study [345] postulated that ATP released from necrotic cells may cause cell death or accelerate APAP-induced cell death. However, subsequently published data, demonstrated in four different types of hepatocytes (human and mouse), could not confirm this concept [346]. Today, one may discuss the unproven possibility that eATP may contribute to APAP-induced cell death via promotion of pyroptotic cell death.

9.5.5.5 Concluding Remarks

Today, the necroinflammation-inducing role of DAMPs in acute liver injury, including drug-induced hepatotoxicity, is well-established. Further investigation is necessary to elucidate precisely the pathogenetic role of DAMPs and their impact on prognosis in this clinical organ injury. Of considerable interest would also be to extend the spectrum of DAMPs that are involved in ALF. Doubtlessly, there are many more DAMPs operating in this fatal disorder than described until today.

9.5.6 SAMPs in Acute Liver Injury

There are only a few reports on the demonstration of SAMPs in acute liver injury. Studies on a model of nonalcoholic steatohepatitis in wild-type and KO mice revealed that macrophage-derived AnxA1 plays a functional role in mitigating hepatic inflammation and fibrogenesis during progression of this disease [347]. Notably, in this study, the authors observed consistently that in vitro addition of recombinant AnxA1 to macrophages isolated from nonalcoholic steatohepatitis livers downmodulates M1 polarization through stimulation of IL-10 production. Also, the cytoprotective effect of PGE2 on the liver has been known for a long time [348]. More recent studies on a model of bile duct ligation in rats showed partial PGE2-mediated immune suppression [349]. Moreover, findings from experiments on a model of acute liver inflammation and injury in transgenic mice suggested that 15-keto-PGE2 from hepatocytes can inhibit inflammatory cytokine production in Kupffer cells and that this paracrine mechanism negatively regulates LPS-induced necroinflammatory response in the liver [350]. In addition, in other lines of studies on a model of LPS/d-galactosamine-induced hepatitis [351], injection of an analog of the SAMP cAMP 1 h before hepatotoxic agents was found to exert a liver-protective effect, as indicated by an increased survival of mice and a significant decrease of plasma alanine aminotransferase level (for cAMP acting as a SAMP, see Sect.
A protective effect of SPMs on acute liver injury has also been reported. Thus, in a murine model of hepatic IRI, RvD1 was found to attenuate IRI-induced hepatocellular damage and the proinflammatory response [352].

Intriguingly, first evidence for the protective action of SAMPs in drug-induced hepatotoxicity has already been reported. Indeed, studies in mice provided first in vivo evidence for a beneficial role of the SAMP PGE2 released upon APAP-induced liver injury [353]. In other lines of studies on thioacetamide-primed rats, hepatic overexpression of the SAMP Anx1 was observed to inhibit APAP-induced expansion of liver injury [354]. Further experiments in this study showed that inhibition of the biosynthesis of this SAMP abolishes this protective effect.

In addition, in studies on mice [355], another SAMP, namely, extracellular adenosine, was also demonstrated to exert a significant protective effect against APAP-induce hepatotoxicity. Plausibly, given these first reports, further studies on SAMPs in APAP-induce liver injury are highly desired.

Together, there is initial evidence for a protective role of SAMPs such as AnxA1, PGE2, cAMP, and SPMs on acute liver injury. Further progress can be expected when SPMs have been investigated in more extensive studies in this research field.

### 9.5.7 Acute Repetitive or Persistent Liver Injury → Chronic Liver Disease/Failure

#### 9.5.7.1 General Remarks

Various chronic liver diseases, triggered by acute repetitive or persistent, infectious or sterile hepatic injuries, can lead—via DAMPs-promoted chronic inflammation in terms of nonresolving inflammatory pathways—to hepatic fibrosis that proceeds to cirrhosis as the final histopathological picture. As a considerable medical burden, various forms of liver fibrosis are known to cause severe morbidity and mortality worldwide. Etiologically, hepatic fibrosis → cirrhosis can arise in consequence of liver-damaging exogenous/toxic, infectious, toxic/allergic, immunopathological/autoimmune, or vascular processes or an inborn error of metabolism, including alcoholic steatohepatitis, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, chronic hepatitis B or C virus infection, and chronic cholangiopathies (for reviews, see [321, 356]).

#### 9.5.7.2 Acute-on-Chronic Liver Failure

A special form of chronic liver diseases is ACLF. This chronic disorder is defined as the acute deterioration of pre-existing chronic liver disease, usually related to an acute precipitating event in terms of an acute infectious or sterile liver injury [285, 286]. Typically, ACLF is observed in patients suffering from cirrhosis that undergoes acute decompensation. The epidemiology, diagnostic criteria, characteristics, clinical course, and prognosis of ACLF have recently been detailed in the CANONIC study, an extensive multicenter European prospective observational investigation in >1000 patients treated for acute decompensation of cirrhosis [357]. Of note,
pathogenetically, ACLF develops in the setting of an exacerbated systemic inflammatory response to initial infectious or sterile acute liver damage, that is, hepatic injuries associated with the emission of MAMPs and DAMPs or DAMPs. As also observed in SIRS associated, for instance, with polytrauma (see Sects. 5.4.2.2 and 8.3.2.2), this hyperinflammatory response is associated with MOF resulting in a high short-term mortality rate [358, 359].

Until to date, the pathogenetic role of MAMPs and DAMPs or DAMPs in ACLF is not firmly proven but intensely proposed and discussed [358, 360]. However, given their documentation in SIRS (see Sects. 5.4.2.3 and 8.3.3), they operate in this acute liver disease most likely and will undoubtedly be described in more detail soon.

9.5.7.3 Pathogenesis of Chronic Liver Disease: Hepatic Fibrosis/ Cirrhosis (in Brief)

There is accumulating evidence suggesting that acute repetitive or persistent insults to the hepatic parenchyma, associated with chronic inflammation in terms of nonresolving inflammation, can result in permanent liver fibrosis → cirrhosis. As outlined in Vol. 1 [1], Part VI, Chpt. 22, and in Sects. 5.5, 6.3, and 6.4, the scenario of inflammation proceeding to fibrosis is orchestrated by multiple cell types, mostly PRM-bearing innate immune cells such as leukocytes, macrophages, and fibroblasts, all of them committed to contributing to the pathogenesis of inflammatory/fibrotic diseases. In the pathogenesis of liver fibrosis → cirrhosis, these cells refer to parenchymal cells, the hepatocytes; the Kupffer cells, i.e., the resident “macrophages” in the liver; and the HSCs, the hepatic “fibroblasts” (Fig. 9.4).

As mentioned above, the hepatocytes and Kupffer cells can be regarded as the targets of any injury since they have been shown to succumb from apoptosis, necroptosis, ferroptosis, and pyroptosis [295–299], that is, subroutines of hepatic insult-induced RCD that serve as productive sources of DAMPs emission.

DAMPs—together with MAMPs in infectious injury—are sensed by PRM-expressing resident Kupffer cells, which trigger NLRP3 inflammasome-dependent and inflammasome-independent signaling pathways to mount an intracellular proinflammatory milieu (including secretion/release of cytokines, chemokines, and adhesion molecules; also compare [295–297, 361–363]). Besides Kupffer cells, other cells such as profibrotic macrophages, neutrophils, DCs, and T/B lymphocytes also contribute to chronic hepatic inflammation—today interpreted as nonresolving inflammation—that is considered to lead to fibrogenesis/fibrosis.

Together, constitutive DAMPs released from cells undergoing RCD as well as inducible DAMPs secreted by activated inflammatory cells (e.g., TGF-β, IL-1β (see below))—together with MAMPs in case of infectious injury—activate PRM-bearing HSCs which transdifferentiate into myofibroblasts (reviewed in [321, 322, 364]). These activated HSCs then, via both serving as the major source of ECM production and interacting with the ECM, drive the mechanisms resulting in liver fibrosis/cirrhosis (Fig. 9.4). This process occurs via epigenetic modifications late in the proliferative phase and is also called activation of myofibroblasts (for details of transdifferentiation into myofibroblasts and epigenetic modifications, see Sects. 6.4, 6.5, and 6.6).
Of note, although HSCs are known as the primary cells responsible for liver fibrogenesis, studies have shown contributing roles for other cells, pathways, and molecules in the development of fibrosis depending on the etiology of liver fibrosis [364–366]. Indeed, the current notions about the complex scenario of fibrogenesis are presented in detail in Chap. 6, including the process of mechanosensing → mechanotransduction mediated by integrins-driven bi-directional “inside-out and outside-in” transmembrane mechanotransduction (symbolized by the two blue/violet-colored bi-directional arrows) leads to progressive liver fibrosis (compare Sect. 6.3 and Fig. 6.1). Constitutive DAMPs are released from necrotic hepatocytes and Kupffer cells, whereas inducible DAMPs are either released from pyroptotic Kupffer cells (IL-1β) or secreted by these cells (TGF-β). Interaction of “myofibroblast-like” HSCs with ECM through integrin-mediated bi-directional “inside-out and outside-in” transmembrane mechanotransduction (symbolized by the two blue/violet-colored bi-directional arrows) leads to progressive liver fibrosis (compare Sect. 6.3 and Fig. 6.1). Constitutitional, ECM extracellular matrix, HSC hepatic stellate cell, IL-1β interleukin-1 beta, IL1R1 interleukin-1 receptor type I, ind inducible, TGF-β transforming growth factor-beta, TβRI/II transforming growth factor-beta receptor I/II. (Sources: [295–297, 302, 321–323, 361–363])

9.5.7.4 DAMPs and SAMPs in Liver Fibrosis
The progression of chronic liver diseases involves chronic parenchymal injury associated with constant RCD-mediated emission of DAMPs, which trigger persistently proinflammatory, profibrotic, and overshooting repairing responses. As outlined in Sect. 6.4.2, several DAMPs such as HMGB1, S100A8, S100A9, and GAL-3, as well as, in particular, TGF-β (denoted as an inducible DAMP in this book) have been reported to drive fibrogenesis. Moreover, the DAMP-driven self-perpetuating
process in fibrosis has been detailed in Sects. 6.4 and 6.5: once MAMP/DAMP-activated myofibroblasts are developed, they take the lead in fibrogenesis via a disastrous ECM/TGF-β-related self-activation process driven by positive feed-forward loops (compare Fig. 6.2).

Constitutive and Inducible DAMPs in Promoting Hepatic Inflammation → Liver Fibrosis

Some distinct constitutive DAMPs involved in liver fibrosis have already been identified and are selectively mentioned here. For example, early in vitro experiments provided already evidence for HMGB1 to activate HSCs [367]. In the context of chronic liver disease, HMGB1 has reportedly been implicated in nonalcoholic steatohepatitis, alcoholic liver disease (ALD), and liver fibrosis (reviewed in [368]). Of interest is the clinical observation that liver HMGB1 protein expression correlates with fibrosis stage in patients with chronic hepatitis C virus infection and primary biliary cirrhosis [369]. Serum levels of HMGB1 were also found to be increased in these patients compared to healthy controls, suggesting secretion of this DAMP. Also, in studies on mice, S100A4 was found to be secreted by a subpopulation of macrophages and to promote the development of liver fibrosis [370]. The authors could show that this DAMP activates HSCs and accumulates in the liver during the progression of liver fibrosis. Further, in studies on mice, the NLRP3-activating IA-2DAMP eATP was shown to potentiate HSC activation (and thus ECM deposition), dependent on P2X7R-mediated NLRP3 inflammasome activation [371] (for NLRP3 inflammasome activation, compare Sect. 2.2.5). Inducible DAMPs have also been reported to activate HSCs. For instance, IL-1β was shown to promote the proliferation of rat HSCs, whereby IL-1 type I receptor (IL1R1), JNK, and AP-1 pathways were observed to be involved in this process [372]. Last but not least, the inducible DAMP TGF-β1 was shown to play a critical role in the development of hepatic fibrosis by triggering the Smad (Smad2, Smad3, Smad4) signaling pathway (known to operate in HSCs) [373] (Fig. 9.4; also compare Fig. 6.3).

SAMPs in Mitigating Hepatic Inflammation → Liver Fibrosis

According to the model of SAMP-promoted resolution of inflammation, the development of liver fibrosis should be decelerated or even prevented by the emission of SAMPs. Indeed, preclinical and clinical evidence suggesting SPMs being able to enhance nonalcoholic steatohepatitis and fibrosis resolution has already recently been reviewed [374]. Although the concept is still not validly proven, preliminary supportive data in this research field were already reported. For example, in studies on the murine model of hepatic IRI mentioned above [352], the interesting finding was observed that RvD1 modulates macrophage polarization in that it attenuates the IRI-induced increase of proinflammatory M1 marker genes in Kupffer cells, associated with a decrease of M2 marker genes. As also observed by the investigators, RvD1 markedly augments the efferocytic activity of Kupffer cells. Together, these findings indicated antiinflammatory and proresolving actions of RvD1, suggesting that this SAMP might interfere with the development of liver fibrosis. A similar concept can be discussed when looking at the studies on a murine model of
nonalcoholic steatohepatitis also mentioned above [347]. In these studies, the authors observed that in vitro addition of recombinant AnxA1 to macrophages isolated from nonalcoholic steatohepatitis livers downmodulates M1 polarization through stimulation of IL-10 production; again a clue that administration of SAMPs might interfere with the development of liver fibrosis.

9.5.7.5 Concluding Remarks
Together, research on DAMPs and SAMPs impacting development of liver fibrosis is still in its infancy. Progress in this field, however, is of great interest because DAMPs as therapeutic targets or SAMPs as therapeutics may be a new therapeutic approach to interfere with the development of liver fibrosis → cirrhosis. This is all the more so, as many experimental data have provided evidence of the reversibility of liver fibrosis [375]. In particular, identification of key DAMPs found to activate/transdifferentiate HSCs as the major drivers of liver fibrogenesis may serve as a potential target of antifibrotic therapy. A future use of SAMPs as therapeutics might also be an option but has still to be proven by appropriate targeted experiments.

9.5.8 Alcohol-Related Liver Injury → Alcoholic Liver Disease

9.5.8.1 General Remarks
Here, the alcohol-related liver injury leading to the development of ALD is separately highlighted because excessive alcohol consumption is a global healthcare problem with enormous social, economic, and clinical consequences. According to the 2018 report of the World Health Organization (WHO) [376], the harmful use of alcohol resulted in an estimated three million deaths (5.3% of all deaths) globally in 2016; these estimates incorporate both the detrimental and beneficial health effects of alcohol consumption. The effects of alcohol consumption on mortality are higher than those of tuberculosis (2.3%), human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) (1.8%), diabetes (2.8%), hypertension (1.6%), digestive diseases (4.5%), road injuries (2.5%), and violence (0.8%). As known, excessive drinking over decades injures nearly every organ in the body. However, the liver sustains the earliest and the highest degree of tissue injury from excessive drinking because this substance of abuse is mainly metabolized by liver cells, which express high levels of two major alcohol oxidizing enzymes, alcohol dehydrogenase, and cytochrome P450 2E1 (CYP2E1) (reviewed in [377, 378]).

Alcoholic liver disease is a major cause of morbidity and mortality from heavy alcohol use and is the leading cause of death from chronic alcohol consumption [379]. The disorder is known as a metabolic liver disease in which pathological progression is largely driven by inflammatory responses. Chronic consumption of alcohol dramatically alters liver function at multiple levels in all liver cell types. As with all other inflammatory diseases, infiltration of PRM-bearing neutrophils is regarded as a hallmark of alcoholic steatohepatitis; however, ALD is also associated with infiltration of many other types of PRM-bearing inflammatory cells.
including Kupffer cells and natural killer T (NKT) cells (for NKT cells, see Vol. 1 [1], Part III, Sect. 8.5.2).

9.5.8.2 Pathogenesis of Alcoholic Liver Disease (in Brief)

Various pathophysiological mechanisms of alcohol-induced tissue and organ injury have been described, including oxidative stress, inflammation, PTMs of proteins, impaired anabolic signaling, upregulation of catabolic processes, and dysregulation in lipid metabolism (reviewed in [47, 48]). Indeed, the pathogenesis of ALD is complex as comprehensively reviewed by Orna et al. [378]; but here only briefly outlined.

The alcohol-induced changes result in a spectrum of liver abnormalities, usually starting with the earliest initiator stage of steatosis, characterized by the deposition of fat in hepatocytes (fatty liver). Beyond fatty liver, ALD consists of a continuum of partly overlapping liver pathologies with variable degrees of (obviously nonresolving) inflammation (steatohepatitis) and progressive fibrosis, associated with excessive deposition of ECM. The fibrotic response begins with active pericellular fibrosis, which may progress to cirrhosis, characterized by excessive liver scarring, vascular alterations, and eventual liver failure. As already stressed above, PRM-bearing Kupffer cells and HSCs have been identified again as the dominating cells in promoting alcohol-induced inflammatory changes and progression to fibrosis and cirrhosis.

While steatosis and inflammation are treatable and reversible upon abstinence, severe alcoholic steatohepatitis and decompensating cirrhosis have a grave prognosis. The pathological progression of ALD is overwhelmingly driven by DAMP-promoted inflammatory processes. Also, as a typical feature of ALD, MAMPs derived from gut microbes, which translocate to the mesenteric lymphatic system and portal circulation, contribute in concert with DAMPs to the establishment of hepatic inflammation (for reviews, see [48, 380]). Moreover, intestinal dysbiotic microbiota and impaired intestinal barrier integrity are additional critical players in the pathophysiology of acute alcoholic steatohepatitis. Such involvement of MAMPs in innate immune inflammatory pathways is facilitated by increased gut permeability, caused by chronic alcohol consumption. This scenario is known to result in higher amounts of LPS in portal and systemic blood of patients with ALD [381, 382] (for the function of LPS as a possible microbe-derived exogenous DAMP in triggering innate immune inflammatory pathways, compare also Sect. 3.2.2 and Vol.1 [1], Part IV, Sect. 11.3). In sum, gut dysbiosis can be considered a critical upstream causal event and an example of organ crosstalk in the pathogenesis of ALD (also compare [383, 384]).

Pathogenetic Role of Regulated Cell Death in Alcoholic Liver Disease

As already described in this chapter, organ injuries usually induce subroutines of RCD that are the main sources of DAMPs emission. This scenario has also been observed in alcohol-related liver injury. Thus, during chronic ethanol consumption, hepatocytes were shown to undergo RCD, including apoptosis, necroptosis, ferroptosis, and pyroptosis (reviewed in [299, 385–387]), which serve as rich sources of
DAMPs in ALD as well. Of interest in this context are recent studies in mice [388], showing that overexpression of the adipose-specific lipin-1 (an enzyme involved in the generation of diacetylglcerol during synthesis of phospholipids and triglycerides) can cause lipid peroxidation and promote ferroptotic liver damage after ethanol administration.

9.5.8.3 DAMPs in Alcoholic Liver Damage

The prototype danger signal HMGB1 is again the most investigated DAMP in ALD, all the more, as liver biopsies from patients with this disorder showed a marked increase in HMGB1 expression and translocation, which correlated with disease stage, compared with healthy explants [389]. In this earlier study, the investigators further demonstrated that HMGB1 increases both in liver and serum from patients with acute alcoholic steatohepatitis superimposed on ALD and cirrhosis and that there is a correlation among the progressive increase in HMGB1 expression, translocation, and secretion with ALD stage in humans. Moreover, in parallel-conducted mouse models of alcohol-induced liver injury, they found that alcohol intake facilitates hepatic and serum HMGB1 expression, translocation from the nucleus to the cytoplasm, and secretion in these animals similar to what they observed in humans [389]. In a clinical study in patients with acute alcoholic hepatitis aimed to identify potential predictive biomarkers (together with MAMPs) for disease severity and clinical outcomes, HMGB1 was evaluated as a potential indicator of disease severity [390]. In this study, the investigators found HMGB1 to be increased in the acute phase of the disease and positively correlated with model for end-stage liver disease (MELD) score (a MELD score is a number that ranges from 6 to 40, based on laboratory tests to assess the urgency for a liver transplant, see [391]). There is also first evidence suggesting a role of the inflammasome in promoting the progression of ALD [392]. This initial suggestion was supported by studies in mice showing that deficiency of NLRP3 prevents the development of alcohol-induced liver inflammation and significantly ameliorates liver damage and steatosis [393]. Further data from this study indicated that ethanol-damaged hepatocytes release uric acid, and eATP, that is, inflammasome-activating IA-2 DAMPs, which are recognized by liver immune cells as inflammatory signals. The authors argued that “the final common pathway of this signaling is most likely represented by the activation of inflammasome, which is required for processing and activation of IL-1β, a key inflammatory cytokine involved in the pathogenesis of alcoholic steatohepatitis…” [393]. More recently conducted studies on alcoholic hepatitis human and animal liver samples and hepatocytes provided evidence demonstrating that alcohol induces pyroptosis of hepatocytes by activating the NLRP3 inflammasome mediated by TXNIP overexpression [394] (for TXNIP, denoted as a metabolic DAMP in this book, acting in NLRP3 inflammasome, see Vol. 1 [1], Part IV, Sect. 13.4.6.3, and Part VI, Sect. 22.4.2.2).

9.5.8.4 Concluding Remarks

Together, ALD comprises a broad spectrum of disease ranging from asymptomatic fatty liver to alcoholic steatohepatitis, progressive fibrosis, and cirrhosis. Again, as
reviewed elsewhere [395] and as also underlined by the tenor of this book, ALD-associated fibrosis reflects an uncontrolled wound healing response to ethanol-promoted liver damage, which is characterized by excessive accumulation of collagen and other ECM proteins. As a pivotal event to develop liver fibrosis, activation of HSCs leads to production of ECM proteins; different cell types such as portal fibroblasts and bone marrow-derived myofibroblasts are also supposed to contribute but to a lesser extent (also compare Sect. 6.2). Together, one can assume that development of liver fibrosis transitioning to cirrhosis represents the work of DAMPs again. Indeed, as comprehensively described in Sects. 6.4 and 6.5, modern notions hold that fibrosis can be regarded as a DAMP-driven self-perpetuating process.

9.5.9 Résumé

Today, the pathogenetic role of DAMPs in acute liver injury → ALF and chronic injury-promoted liver fibrosis is well documented, whereas the role of SAMPs has still to be investigated more precisely to draw firm conclusions. Also, preclinical and clinical studies have clearly revealed a critical role of DAMPs in ethanol-induced injury to the liver. Moreover, it should not be forgotten to mention here that, besides alcohol, intoxications can be caused by poisons. An impressive example is the mushroom poisoning of the liver that can lead to acute liver injury and ALF [396]. Identification of DAMPs involved in this disease and their use as therapeutic targets will undoubtedly extend the therapeutic armamentarium to be applied in this potentially life-threatening liver injury.

Indeed, for clinicians working in ICUs, the routine measurement of DAMPs and SAMPs as diagnostic and prognostic biomarkers in those patients may become an exciting option soon. Intense clinical studies examining the pattern of DAMP and SAMP emission and tentatively defining a homeostatic DAMP/SAMP signature in those patients may not only assist in predictive risk modeling and reduction in morbidity and mortality but might also be helpful in making the right and reasonable therapeutic decision. The questions to get correctly answered are at what exact stage of a severe liver damage to start and to stop inhibition of DAMPs, and when to begin and discontinue application of SAMPs, questions that also apply to patients with a different solid organ injury.

9.6 Acute and Chronic Pancreas Injury

9.6.1 Introductory Remarks

Pancreatic injuries are well-known to abdominal surgeons as an acute traumatic injury and to gastroenterologists as an acute or chronic alcohol-related injury. Traumatic injuries to the pancreas are rare and difficult to diagnose. They are usually subtle to identify by different diagnostic imaging modalities, and these injuries are often overlooked in cases with extensive multiorgan trauma. The most evident
findings of pancreatic injury are posttraumatic pancreatitis with blood, edema, and soft tissue infiltration of the anterior pararenal space (reviewed in [397]). However, this is not the theme of this section. Instead, here, focus is directed on alcohol-related pancreatic injury, which is one of the most common causes of both acute and chronic pancreatitis (comprehensively reviewed by Klochkov and Sun in [398]).

9.6.2  Acute Alcohol-Related Pancreatic Injury → Acute Pancreatitis

9.6.2.1 General Remarks
Acute injury-induced pancreatitis is a necroinflammatory disease resulting from exocrine cell destruction by infiltrating inflammatory cells. Acute pancreatic inflammation will either resolve with the pancreas fully regenerating, lead to transient organ failure, or progress to cause systemic inflammation and MOF. Although commonly associated with pancreatitis, alcohol alone is unable to trigger pancreatitis. Instead, alcohol and its metabolic byproducts are supposed to predispose the pancreas to injuries from agents that generally do not (or only mildly) cause pancreatitis (for reviews, see [398–400]).

9.6.2.2 Pathogenesis of Acute Pancreatitis (in Brief)
As reviewed [398, 400], the complete pathogenesis of this disease is not entirely known but is supposed to originate from alcohol’s effects on the small pancreatic ducts and acinar cells. The pancreas uses oxidative and non-oxidative metabolism to process alcohol. The oxidative pathway leads to the formation of acetaldehyde that causes detrimental effects in acinar cells through activation of stellate cells and increased expression of proinflammatory cytokines. The non-oxidative path requires the formation of fatty acid ethyl ester synthase, which leads to activation of key transcription factors, sustained increases in intracellular calcium, and inhibition of ECM, finally resulting in further cell injury. Moreover, alcohol also promotes premature activation of trypsinogen and other digestive and lysosomal enzymes within the acinar cells, thereby promoting the pancreatic tissue to auto-digest. The whole scenario contributes to aggravation of pancreatic inflammation. Another contributing mechanism is intra-acinar activation of NF-κB that further drives the inflammatory response. The NF-κB-mediated inflammatory response appears to be typically associated with acute pancreatitis, as well as the potentially fatal SIRS as the worst outcome of this disease.

In other words and from the perspective of this book, the scenario of alcohol-induced pancreatitis reflects the work of local emission of DAMPs which might systemically be released in case of SIRS/MOF (a topic that “cries for proving determinations”!).

9.6.2.3 Concluding Remarks
The incidence of acute pancreatitis is increasing, and alcohol is still recognized as one of the most common causes. A tremendous amount of work has provided evidence of several mechanisms by which ethanol and both its oxidative and
non-oxidative metabolites damage pancreatic cells. In this context, Clemens et al. [400] concluded: “By understanding the mechanisms by which ethanol alter the normal physiology of the pancreas, we have uncovered potential targets for therapeutic intervention. Further experimental work and clinical studies are required to determine the utility of these targets in treating alcoholic pancreatitis.” Again, it can be expected that the measurement of ethanol-induced emission of DAMPs will contribute to progress in this therapy.

9.6.3 Acute Repetitive or Chronic Alcohol-Related Pancreatic Injury → Chronic Pancreatitis

Chronic pancreatitis is believed to result from recurrent attacks of acute pancreatitis. Although alcoholic pancreatitis can remain an acute disorder, in many cases, this acute disease progresses to chronic alcoholic pancreatitis. Notably, it was reported that such a progression from acute to chronic pancreatitis is most common in habitual alcohol abusers, indicating that excessive alcohol consumption is involved in acute pancreatitis progressing to a chronic fibrotic disorder (reviewed in [400]).

Typically, chronic pancreatitis is a syndrome characterized by chronic progressive pancreatic inflammation (obviously in terms of nonresolving inflammation) that progresses to fibrosis and scarring, resulting in loss of exocrine (acinar), endocrine (islet cells), and ductal cells [401]. The pathogenesis of chronic alcoholic pancreatitis is poorly understood, but current notions hold that chronic alcohol consumption sensitizes the acinar cell to injury by interfering with mechanisms that protect against ER stress. The alcohol injury-induced complex chronic inflammatory disorder that is linked to genetic, metabolic, and environmental factors leads to the development of pancreatic insufficiency, steatorrhea, diabetes, pancreatic calcification, and fibrosis (reviewed in [402]).

9.6.4 DAMPs in Alcohol-Induced Pancreatitis

Of note, the emission of DAMPs has already been observed in experimental alcoholic pancreatitis. In earlier experiments on a rat model of acute alcohol-induced pancreatitis, nuclear release of HMGB1 was seen as a feature of necrotic cell death [403]. In similar experiments on alcohol-fed rats, tissue release of HMGB1 was found to be correlated well with the systemic necrosis marker lactate dehydrogenase [404]. Also, in investigations on ethanol-induced pancreatic injury using a mouse model of binge ethanol exposure, the authors detected release of HMGB1 from necrotic cells [405]. Certainly, the list of DAMPs involved in this disease is still small but can be expected to increase shortly. In fact, regarding the role of DAMPs in other forms of acute pancreatitis [406], their pathogenetic role in this (sometimes life-threatening) disorder cannot be overestimated.
9.6.5 Résumé

In summary, preclinical and clinical studies have revealed a critical role of DAMPs not only in ethanol-induced injury to the brain and liver but also—as briefly touched here—to the pancreas. Thus, this research field appears to require broader clinical and practical attention. For example, in the case of acute severe alcoholic pancreatitis, inhibition of DAMPs involved may even help save the patient’s life. It can be expected that, in the future, gastroenterologists will get familiar with the new approach of treating this excessive alcohol consumption-induced disorder.

9.7 Traumatic Musculoskeletal Injury Affecting Remote Organs

9.7.1 Introductory Remarks

As any organ injury, severe musculoskeletal trauma can trigger an inflammatory response, and an excessive hyperinflammatory response is known to result in SIRS and MOF, an exciting observation that deserves to be briefly addressed in this chapter.

A peculiar feature of musculoskeletal trauma is the historical observation that it can lead to a “secondary injury” affecting distant organs, also referred to as the secondary injury model. As reviewed [407], this pathophysiological model was originally developed more than 40 years ago. In this model, acute trauma is denoted as the primary injury, “whereas secondary injury refers to damage to otherwise uninjured cells that was a direct consequence of the physiologic response to primary injury. In the original model, mechanisms for secondary injury were hypothesized based on then-contemporary understandings of Immunology and cellular pathology.” Today, this model can be easily explained by systemic release of locally emitted DAMPs into the blood circulation. In the following, a few examples of this phenomenon are addressed by choosing bone fracture and soft tissue injury, promoting remote organ injuries.

9.7.2 Bone Fractures and DAMP-Promoted Remote Organ Injuries

9.7.2.1 General Remarks

Early studies already showed that bone fractures, eventually associated with soft tissue injury, play a pivotal role in the induction of systemic inflammation and remote organ dysfunction after fracture. For example, experiments using a murine model of bilateral femur fracture alone or in combination with soft tissue injury affecting the thighs revealed that each injury promoted systemic inflammation, but the combination of both injuries was required to induce marked remote liver dysfunction associated with systemic inflammation [408]. Intrinsically, any bone
fracture leads to emission of bona fide DAMPs, which initiate a healing efferent innate immune response. Again, there is a double role of DAMPs in case of bone fracture: local emission promotes fracture healing (see Sect. 8.2.3 [409]), and massive emission and systemic distribution may lead to remote organ injuries such as TBI and ALI. Indeed, earlier experimental studies have already demonstrated an increase in cytokines within human fracture site hematomas, as well as in the systemic circulation of patients sustaining fracture [410]. Research in this field of traumatic lesions is at the beginning. However, a few reports have been published which are briefly quoted here.

9.7.2.2 Pathophysiology of Bone Fractures (in Brief)
Under homeostatic conditions, bone fracture heals up in the course of a DAMP-promoted physiological inflammatory innate immune process. However, in massive multiple fractures often associated with soft tissue damage, pathophysiological mechanisms in terms of systemic inflammation and remote organ injuries, associated with cytokine release, have been described [411–414]. Current knowledge now holds that delivery of large amounts of DAMPs in the blood circulation promotes systemic inflammation by affecting susceptible organs such as the brain and the lung. In the following, this topic is briefly reviewed by describing selected DAMPs involved in this process.

9.7.2.3 DAMPs Emission in Bone Fractures
Though only a limited number of DAMPs in this research field has been investigated, the data of the published studies are convincing and have contributed to more knowledge of the pathophysiology of TBI and ALI, especially in the understanding of the cascade of their complications.

High Mobility Group Box 1
In a model of bilateral femur fracture in TLR4 wild-type mice, treatment with antibodies to HMGB1 was found to cause a suppression of circulating IL-6 and IL-10 and lower serum alanine aminotransferase levels, indicating a pathogenetic role of HMGB1 in this model of trauma-induced inflammation [415]. According to the authors’ conclusion, these data demonstrate a critical role for an HMGB1 → TLR4 pathway in the initiation of systemic inflammation and end-organ injury following isolated peripheral tissue injury. More recent experiments on a model of closed fracture musculoskeletal injury in mice supported these data by demonstrating that the upregulated expression of HMGB1 mRNA after injury—indicating infliction of sterile inflammation—could be significantly decreased by intravenous injection of lidocaine [416]. In other sets of studies on a murine model of tibia bone fracture one day after experimental stroke induction, intraperitoneal injection of neutralizing anti-HMGB1 antibodies was found to attenuate the bone fracture-mediated inflammatory effects on the cerebrum [417]. According to the authors’ conclusion, these findings suggest that bone fracture shortly after stroke enhances stroke injury via augmented inflammation through HMGB1. These experimental observations could be confirmed by further studies on a bone fracture/TBI model in mice (already
mentioned above), demonstrating that bone fracture can stimulate the inflammatory cytokines releases and exacerbate TBI symptoms [49]. Notably, HMGB1 was dramatically elevated by bone fracture, and the severity of TBI was reduced after blocking HMGB1. Given these data, the authors suggested that HMGB1-mediated inflammation may have a substantial impact on the secondary TBI.

Mitochondrial DNA

Mitochondrial DNA belongs to the few DAMPs investigated in the context of fracture-mediated remote organ injury. Thus, in studies on a model of hip fracture in rats mentioned above, mtDNA was found to induce ALI [120]. In the first part of the experiments, the effects of hip fracture were investigated; in the second part, the impact of intravenously injected mtDNA on the animals. The experimentally set fracture resulted in significant mtDNA release, TLR9 → NF-κB expression, and lung injury, whereas the mtDNA injection could indirectly induce pulmonary damage. The investigators concluded that these results suggest the lung injury to be induced by hip fracture, probably under involvement of the mtDNA → TLR9 → NF-κB pathway.

9.7.3 Soft Tissue Injury Promoting Remote Organ Injuries

A severe form of soft tissue injury is exemplified by rhabdomyolysis that can be caused by direct traumatic injury as a result of drugs, toxins, infections, muscle ischemia, electrolyte, and metabolic disorders. The disease is a complex medical condition involving the rapid dissolution of damaged or injured skeletal muscle. Of note, rhabdomyolysis is reportedly associated with high morbidity and mortality when subsequently promoting the development of AKI in the days following initial presentation and develops in 33% of patients. It is well accepted that AKI is the result of an accumulation of myoglobin, which is nephrotoxic. Hypovolemia is another associated factor that leads to renal hypoperfusion (reviewed in [418, 419]). Notably, there is first evidence suggesting myoglobin may contribute to rhabdomyolysis-induced AKI via the TLR4 → NF-κB pathways [420]. However, whether myoglobin acts as a DAMP in this scenario to be sensed by TLR4 has still to be confirmed in other targeted experiments.

9.7.4 Résumé

In a chapter on the role of DAMPs in solid organ injuries, the topic of musculoskeletal injuries affecting remote organs is of high interest. Indeed, the documentation of locally emitted DAMPs to promote remote organ injuries is an impressive example of the property of these molecules—when released into the blood circulation—to spread out systemically and function in any part of the body. As outlined above (Sect. 8.3.3), this scenario can culminate in SIRS when DAMPs are produced in excess.
Of note, this phenomenon is not restricted to the two examples mentioned here and appears to be a general fundamental event. For instance, another similar scenario refers to postoperative remote lung injury (e.g., ARDS) that has been observed to occur following various surgeries and is associated with short- and long-term morbidity and mortality [421]. Here again, the release of DAMPs may trigger a systemic inflammatory response, which ultimately results in organ injury, including lung injury: undoubtedly, another field of using DAMPs as biomarkers and therapeutic targets!

9.8 Biomechanical Injury to Articular Cartilage → Osteoarthritis

9.8.1 Introductory Remarks

More in terms of an appendix and in passing, injury-induced (sterile) osteoarthritis (OA) should be added to the list of solid organ injuries, addressed in this chapter. Biomechanical injuries to articular cartilage are thought to be pathogenetically involved in this degenerative bone/joint inflammatory process. Indeed, the articular cartilage resides in a complex and dynamic mechanical environment in vivo, characterized by compressive and shear stresses along multiple axes and hydrostatic and osmotic pressures throughout (reviewed in [422, 423]).

The chronic arthropathy, characterized by progressive destruction of articular cartilage, remodeling of the underlying bone, formation of ectopic bone, hypertrophy of the joint capsule, and inflammation of the synovial lining, is a common disease that can affect joints from any part of the body, in particular, the knee, hip, and shoulder, and represents a major cause of disability and joint pain worldwide. As known to every physician, female gender, elderly people, and obese individuals show high susceptibility to this joint disease [424–426].

9.8.2 Regulated Cell Death

It is soundly imaginable that aberrant acute repetitive or chronic articular cartilage load may lead to any form of RCD. And indeed, for example, apoptosis has been reported to occur in osteoarthritic cartilage, whereby, however, the relative contribution of chondrocyte apoptosis in the pathogenesis of OA was challenging to evaluate, and contradictory reports exist on the rate of apoptotic chondrocytes in osteoarthritic cartilage [427].

On the other hand, convincing evidence from studies on a cartilage trauma model has been provided for the involvement of necroptosis in OA disease [428]. Moreover, in this study, the investigators found a possible link between cartilage injury and necroptotic processes, depending on oxidative stress and cytokine release.

Also, other lines of studies revealed a vital role of synovial fibroblast pyroptosis in the onset and development of knee OA. An orienting study on fibroblast-like
synoviocytes provided already first evidence for a pathogenetic role of NLRP3 inflammasome-related pyroptosis in knee OA [429]. In a subsequent study on a knee OA model in rats, the same investigator group provided evidence for synovial macrophage pyroptosis to participating in the pathological process [430].

Although ferroptosis has not been described to occur in OA so far, one may assume that this subroutine of RN also takes place given the knowledge that oxidative stress and lipid peroxidation are pathogenetically involved in this disorder [431, 432].

Together, there is first evidence indicating involvement of various subroutines of RCD in the pathogenesis of OA, which—as definitely documented in other injury-promoted inflammatory disorders—may serve as sources of DAMPs emission.

9.8.3 Pathogenesis of Osteoarthritis (in Brief)

Accumulating evidence suggests OA to reflecting a multifactorial disorder in which low-grade, chronic inflammation in terms of nonresolving inflammation—and not chronic degenerative processes as previously thought—plays a central role, whereby the synovitis is characterized by infiltration of inflammatory cells into the synovium. In the inflamed joint tissues and fluids, the full palette of inflammatory mediators has been identified, including cytokines, chemokines, and growth factors. These mediators can be produced by different cell types within the joint such as macrophages, fibroblast-like synoviocytes, chondrocytes, and resident or infiltrating immune cells.

Moreover, there is also increasing evidence for joint injury-emitted DAMPs to promote these sterile inflammatory processes (reviewed in [425, 433, 434]).

9.8.4 DAMPs in Osteoarthritis

Already very early, a first report on the role of DAMPs in OA was published by Sokolove and Lepus [435]. In their review, the authors discussed ECM-derived DAMPs (biglycan, fibronectin, HA, TNC), HMGB1 and S100 proteins, and crystals released from cartilage. In a subsequent review [436], the scenario of DAMP-activated macrophages in OA was highlighted. Among others, the authors discussed that the damage caused to chondrocytes by activated macrophages would lead to the release of more DAMPs, creating a positive feedback loop that leads to the continued destruction of cartilage. More precise knowledge about OA-associated DAMPs was added by more recent studies. For example, in experiments on human monocyte-derived macrophages, it could be demonstrated that basic calcium phosphate crystals can polarize primary human macrophages toward an M1-like phenotype sustaining proinflammatory processes [437].

9.8.5 Résumé

Together, there is no doubt that DAMPs are heavily involved in the pathogenesis of OA and may even explain the pathogenetic complexity of the inflammatory mechanisms discovered in this disorder. Future work is needed to fully define the
DAMP-triggered molecular pathways mediating the low-grade inflammation in OA and, even more important, to uncover a potential insufficient role of SAMPs that may contribute to the nonresolving nature of this inflammation. If such data are available, the value of using intra-articular DAMPs as therapeutic targets or administering SAMPs intra-articularly could be evaluated as future therapeutic approaches in OA.

9.9  DAMPs and SAMPs as Diagnostics, Prognostics, Therapeutics, and Therapeutic Targets in Solid Organ Injury

9.9.1  Introductory Remarks

During recent times, as already known for polytrauma, an increased interest in the use of DAMPs and SAMPs as biomarkers and therapeutic targets for specific organ injuries can be noted. As discussed in the previous chapter, in polytraumatized patients, DAMPs and SAMPs can be seen as the origin of the development of both SIRS and CARS and are therefore promising molecules as biomarkers for patient stratification and as therapeutic targets and therapeutics. By contrast, in patients suffering from organ-specific injuries, for example, TBI, the determination of DAMPs and SAMPs will give individual information about the severity of the injury, their possible remote effects, and early signs of either controlled healing or uncontrolled disease-causing processes. Also, identification of such biomarkers could allow improved understanding of the pathological processes involved in organ-specific injury and may be helpful in diagnosis, prognostication, and development of novel therapies. In fact, the application of DAMPs and SAMPs as biomarkers is expected to improve the speed of clinical decision-making, in particular, in designing and executing patient-individualized treatment strategies.

Some of those topics were already briefly or partly touched in the running text. Here, the published literature is reviewed—well aware that this is just the begin of the development of a new era of monitoring in solid organ injuries.

9.9.2  DAMPs and SAMPs as Diagnostic and Prognostic Biomarkers

9.9.2.1  General Remarks

As said, monitoring of DAMPs and SAMPs in organ-specific injury has gained increasing attention regarding their function as valuable biomarkers. Indeed, currently used routine biochemical biomarkers of organ damage mostly inform physicians in a delayed fashion, when the organ-specific damage is too advanced or even irreversible. Such traditional biomarkers include glial fibrillary acidic protein for brain injury; serum creatinine and kidney injury marker-1 for kidney injury; serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase for liver injury; cardiac troponin for heart damage; intestinal-type fatty acid-binding protein for gut injury; and D-dimer for coagulopathy (compare also review in [408]).
The routine sequential determination of DAMPs and SAMPs, however, may represent an early prognostic sign as to whether a given acute infectious or sterile organ injury will result in a normal healing, inflammation-promoting → inflammation-resolving response or may proceed—via nonresolving inflammatory/fibrotic processes—to acute and/or chronic organ failure. Accordingly, the use of DAMPs in addition to such “familiar” biomarkers may contribute to a sophisticated application of criteria of personalized medicine that strives for improvements in tailoring and timing of diagnostic, prognostic, preventive, and therapeutic measures.

### 9.9.2.2 Traumatic Brain Injury

Most work on DAMPs in their function as biomarkers in TBI has been reported regarding S100 proteins. For example, as already mentioned above, in an analysis of serum levels of S100B proteins in pediatric patients with TBI, median serum levels of S100B at admission were shown to decrease significantly 1 week after TBI [74]. Follow-up of these patients revealed that serum levels of this DAMP 1 week after injury in patients with unfavorable 6-month outcomes were substantially higher than levels 1 week after injury in patients with favorable outcomes. The authors concluded that serial measurements of serum S100B may help assess brain damage and clinical outcome of pediatric patients with TBI. The increasing importance of S100B proteins acting as biomarkers in TBI has also been discussed and reviewed elsewhere (see [438–440]).

Additionally, as already mentioned earlier, levels of HMGB1 could be measured in the CSF of adult patients with TBI [59] whereas, in pediatric patients, the CSF levels of HMGB1 were found to be even predictive for outcome [67]. Moreover, an observational clinical study in patients with severe TBI revealed that the plasma HMGB1 concentration can be successfully used as a novel biomarker for significantly predicting 1-year mortality and unfavorable outcome of TBI [66]. These findings were confirmed by recent reports on the role of HMGB1 as a viable biomarker in TBI, as published elsewhere [55, 441]. There is agreement among the authors that HMGB1 is a promising prospective candidate for future studies, which should explore the predictive value of this DAMP in TBI.

Also, as already touched above [70], mtDNA measured in the CSF of children with severe TBI has been proposed to be a useful biomarker that correlates with neurological outcome after TBI.

Interestingly, time seems to be mature for SAMPs to join the scene. Thus, an experimental study on a model of TBI in mice provided initial evidence for SPMs, to be used as biomarkers [82] (see below under SAMPs as therapeutics).

### 9.9.2.3 Acute Lung Injury

As already mentioned in Sect. 8.3.5, DAMPs have reportedly also been explored as promising biomarkers in ALI [132–135]. Thus, informative HMGB1 levels could be measured in bronchoalveolar lavage fluid of trauma patients during mechanical ventilation and ventilator-associated pneumonia [134]. In a more recent study on
patients with severe pneumonia and ARDS requiring mechanical ventilation [135], the investigators remarkably observed the day 1 HMGB1 concentration to be a critical, independent biomarker for ICU mortality. Other DAMPs were also explored. For example, in studies on ARDS patients, plasma and bronchoalveolar lavage fluid extracellular histone levels were found to be much higher in ARDS patients than in healthy controls [145]. The extended analysis of the clinical data revealed a significant association between extracellular histones and ARDS severity and mortality. Also, extracellular histones were shown to be correlated with an evident systemic inflammation detected in ARDS patients. The authors concluded [145] that “extracellular histones in ARDS patients are excessively increased and may contribute to disease aggravation by inducing cellular damage and promoting systemic inflammation.”

Moreover, as already mentioned in Sect. 9.3.5.4, in a clinical study on patients with suspected ventilator-associated pneumonia, higher levels of mtDNA were detected in the bronchoalveolar lavage fluid [142]. In another clinical study conducted by the same group, mtDNA in transfusion products was suggested to contribute to the development of ARDS after multiple transfusions [119]. These findings certainly enrich the list of DAMPs to be harnessed as biomarkers in ALI. The authors of this study concluded [119]: “Finally, to determine the true value of serum mtDNA DAMP measurements as predictive biomarkers for the evolution of ARDS and MODS in the setting of severe injury, it will ultimately be necessary to standardize means for measuring and reporting mtDNA abundance and apply these to a substantial patient cohort.”

9.9.2.4 Acute Kidney Injury

In a recently reported clinical study on pediatric patients suffering from AKI, S100A8/S100A9 was detected in the urine and proposed by the authors to use as a biomarker for the prediction of adverse outcome requiring renal replacement therapy [239]. A similar proposal for applying S100A8/S100A9 as a diagnostic and prognostic biomarker in intrinsic AKI was made elsewhere [240]. Also, in a clinical study on patients with AKI, mtDNA was measured in the urine, the severity of the disease was quantified, and patients were followed for 90 days [242]. As reported from the authors, the measured urinary mtDNA levels turned out to be a marker of AKI severity, as reflected by its significant correlation with the peak serum creatinine level, duration of hospital stay, and probably the need for temporary dialysis. Thus, like other DAMPs, urinary mtDNA has also the potential to serve as an essential biomarker of AKI. In similar clinical studies on surgical critically ill patients [442], elevated urinary mtDNA levels could identify newly developed AKI and predict renal replacement therapy or hospital mortality in those patients. Finally, the use of urinary mtDNA as a biomarker of renal dysfunction could be confirmed in patients with AKI following cardiac surgery [443]. Postoperatively, the investigators found that urinary mtDNA was associated with increased risk of worsening AKI following initial sample collection and that this DAMP predicts AKI progression by receiver operator characteristic analysis.
9.9.2.5 Acute Liver Injury

DAMPs such as HMGB1, nDNA, and mtDNA have already been used as biomarkers in APAP intoxication/hepatotoxicity and showed a good correlation with the course of this acute liver disease [304]. Remarkably, as a typical result of clinical studies, measurement of plasma levels of HMGB1 reportedly surpasses all other biomarkers to predict clinical outcome for APAP-overdosed patients [333, 444]. Importantly, the systemic HMGB1 release from the APAP-induced liver injury was observed to be biphasic. One may discuss that this observation nicely documents the initial injury-induced passive release of HMGB1 as a constitutively expresses IA-1 DAMP, followed by active secretion of acetylated, disulfide HMGB1 as an inducible IIB-2 DAMP via DAMP-activated innate immune cells (see also Table 3.1 and Vol. 1 [1], Part IV, Sect. 11.2). In this context, it is worth mentioning even a report on a significant increase in plasma HMGB1 in patients with acute alcoholic hepatitis [390] that was appreciated by the authors as a potential biomarker that will improve the prediction of disease progression and survival in ALD.

9.9.2.6 Concluding Remarks

The few selected examples of DAMPs in their role as biomarkers, as described here, can be regarded as the beginning of a new era in monitoring injury-induced organ-specific diseases. In principle, every DAMP documented to play a critical pathogenetic role in solid organ injury can be harnessed as a diagnostic/predictive/prognostic biomarker. However, as already stressed in Sect. 8.4.2.4, instead of concentrating on one DAMP as a biomarker, a distinct pattern of several DAMPs will probably turn out to be more instructive in predicting the outcome of organ injury in different types of patients. This endeavor presupposes, however, that typical DAMP patterns in different patient categories must first be explored.

However, as progress in this research field moves forward, SAMPs (still better “SAMP patterns”) are supposed to accompany the DAMPs as biomarkers sooner or later. The first evidence for such a concept is already available. For example, in studies in pediatric patients with severe TBI, the concentration of the SAMP adenosine in CSF was observed to be increased in a time- and severity-dependent manner in infants and children after severe head injury [84]. More precisely, and as already stressed in Sect. 7.3.3 and Fig. 7.1, the determination of a DAMP/SAMP ratio in terms of a DAMP/SAMP signature appears to be the most accurate parameter to monitor the course and the outcome of an individual organ injury. Indeed, one is tempted to speculate that each organ-specific injury is marked by a specific DAMPs/SAMPs pattern. Accordingly, continuous tracing of the DAMP/SAMP ratio might turn out to emerge to an essential future parameter in reflecting the status of injured organs.

9.9.3 DAMPs as Therapeutic Targets and SAMPs as Therapeutics

9.9.3.1 General Remarks

In principle, the therapeutic application of DAMPs or SAMPs in solid organ injuries is to prevent the pathological consequences (e.g., hyperinflammatory, chronic inflammatory → fibrotic responses) without interfering with the homeostatic
healing processes. In the case of isolated organ injury, this means to prevent the
development of a potentially life-threatening organ-specific acute disease such as
ARDS (acute organ failure) or a chronic inflammatory/nonresolving → fibrotic dis-
ease (chronic organ failure).

Again, for future optimal treatment modalities, the exact status of the DAMP/
SAMP ratio as a guide in tailoring treatment options might be necessary to be deter-
mined for each organ injury (e.g., a priori to be established by targeted studies and
increasing experience in large cohorts of patients). This would allow precise and
timely intervention after the onset of the disorder, that is, appropriate inhibition of
DAMPs and administration of SAMPs, aimed at reaching full restitution ad integrum.

On the basis of preclinical studies on suitable experimental models, initial pro-
posals of harnessing DAMPs (less SAMPs) as future therapeutic targets in isolated
acute organ injury have already been communicated. Also, antagonists of DAMPs
are in development for clinical use, as previously addressed in Sect. 8.4.4.2. Here,
some recent publications on their use in solid organ injuries are briefly cited.

### 9.9.3.2 Blockade of DAMPs in Acute Organ Injuries

The theoretical background of interventions in acute isolated organ injuries differs
from that as outlined for interventions in polytrauma in that a hyperresolving/immu-
nosuppressive phase is not relevant. Instead, the therapeutic imperative strives for
the prevention of an injury-induced hyperinflammatory state that may lead to acute
organ dysfunction or even failure. Accordingly, a blockade/elimination of DAMPs
or administration of SAMPs has to be taken into consideration.

**Blockade of DAMPs in Traumatic Brain Injury**

The blockade of HMGB1 has been successfully applied in several models of acute
organ injury. In studies on rats already mentioned above, administration of an anti-
HMGB1 mAb after TBI was shown to remarkably inhibit fluid percussion-induced
brain edema [56]. This effect was associated with inhibition of HMGB1 transloca-
tion, protection of BBB integrity, suppression of inflammatory molecule expres-
sion, and improvement of motor function. Also, in a murine TBI model, blockade of
HMGB1 by an HMGB1 A-box fragment (an antagonist competing with full-length
HMGB1 for receptor binding) was shown to reverse brain damages in the mice fol-
lowing TBI [445]. The experiments further revealed that the antagonist could sig-
ificantly reduce brain edema by protecting the integrity of the BBB, ameliorate cell
degeneration, and decrease expression of proinflammatory cytokines released in the
injured brain after TBI. These cellular and molecular effects were accompanied by
improved behavioral performance in TBI mice. The authors of these experiments
suggested from their data [445] that HMGB1 A-box may have therapeutic potential
for the secondary brain damages in TBI. In another study on a murine model of
olfactory nerve transection, injection of an anti-HMGB1 antibody was shown to be
associated with significantly smaller areas of injury-associated tissue, fewer astro-
cytes and macrophages/microglia, and an increase in regenerating nerve fibers
[446]. Given these findings, the investigators proposed that inhibition of HMGB1
could provide a new therapeutic strategy for the treatment of olfactory dysfunction
following head injuries. Also, as documented by other lines of studies on a rat TBI
intravenous injection of an anti-HMGB1 mAb can attenuate accumulation of activated microglia in the rat cortex in the ipsilateral hemisphere after TBI. Moreover, these experiments showed that anti-HMGB1 mAb inhibits HMGB1 translocation, suppresses impairment of motor function, and has positive effects on electroencephalography activity. In their conclusion, the investigators argued that anti-HMGB1 mAb may prevent cognitive dysfunction after TBI. In the context of these reports, a study on glycyrrhizin, an inhibitor of HMGB1, is also of interest [448]. In these experiments, glycyrrhizin was used to investigate whether the inhibition of this DAMP could modulate microglia/macrophage polarization after TBI. The results obtained showed that treatment with this inhibitor ameliorates the neurological function recovery, reduces the lesion volume, and inhibits the release and expression of HMGB1 after TBI. Further, the investigators observed that the administration of this substance could suppress M1 phenotype activation and promoted M2 phenotype activation of microglia/macrophages. Given their interesting findings, the authors suggested that glycyrrhizin mitigates TBI by inhibiting M1 phenotype while promoting M2 phenotype activation of microglia/macrophages, at least partly through inhibiting HMGB1 [448].

**Blockade of DAMPs in Acute Lung Injury**

As outlined in Sect. 8.3.5.2, several experiments have convincingly proven a beneficial effect of HMGB1 inhibition in mitigating ALI [127–131]. In one of those cited studies on a mouse model of hyperoxic inflammatory lung injury [127], inhibition of HMGB1 by neutralizing anti-HMGB1 antibodies, administrated before or after onset of the hyperoxic exposure, was found to mitigate pulmonary edema and inflammatory responses significantly. The authors concluded that—if these results could be translated to humans—“they suggest that HMGB1 inhibitors provide treatment regimens for oxidative inflammatory lung injury in patients receiving hyperoxia through mechanical ventilation.” Similar observations were made in studies on a paraquat-induced ALI, in which blocking of HMGB1 signaling by glycyrrhizin was shown to dramatically inhibit the infiltration of neutrophils and attenuate lung injury [449]. In this context, studies on a rat model of crush injury are of interest showing that intravenous administration of anti-HMGB1 antibody was associated with amelioration of histological findings of lung damage [450].

**Blockade of DAMPs in Acute Kidney Injury**

As also mentioned above, neutralizing HMGB1 with an anti-HMGB1 antibody was shown to ameliorate chronic CsA nephrotoxicity via inhibition of the TLR4 signaling pathway [236]. Moreover, the mitigating effect of the functional HMGB1 inhibitor glycyrrhizin on TBI could also be demonstrated in AKI. In an experimental model of renal IRI [451], glycyrrhizic acid was shown to reduce the hypoxia-induced death of tubular EpCs. The authors discussed that inhibition of the interaction of HMGB1 with tubular EpCs through this substance may represent a therapeutic strategy for the attenuation of renal injury following renal IRI. In other sets of studies on the model of folic acid-induced renal damage [452], melatonin pretreatment was shown to improve cell cycle arrest of tubular EpCs. Notably, this
protective function of melatonin was observed to be closely related to the inhibition of nucleocytoplasmic translocation of HMGB1 in tubular EpCs. Further, as already touched above, extended experiments of the Anders group on AKI models revealed that neutralizing anti-histone IgG can suppress intrarenal inflammation, neutrophil infiltration, and tubular cell necrosis and improve renal excretory function [245].

**Blockade of DAMPs in Acute Liver Injury**

A beneficial effect of HMGB1 inhibition could also be shown in models of acute liver injury. For example, in studies on a mouse model of APAP overdose, blockade of HMGB1 by an anti-HMGB1 antibody was found to significantly improve hepatocyte regeneration, associated with decreased serum transaminases, reduced number of hepatic infiltrating inflammatory cells, and restored liver structure [329]. In similar studies on the same model, blockade of HMGB1 by a partly humanized mouse anti-HMGB1 mAb was found to mitigate APAP-induced serum elevations of alanine aminotransferase significantly and abrogate markers of APAP-induced inflammation completely [330]. The authors concluded: “This is the first report describing the generation of a partly humanized HMGB1-neutralizing antibody with validated therapeutic efficacy and with a prolonged therapeutic window, as compared to NAC, in APAP-ALI. The therapeutic effect was mediated by HMGB1 neutralization and attenuation of postinjury inflammation. These results represent important progress toward clinical implementation of HMGB1-specific therapy as a means to treat APAP-ALI and other inflammatory conditions” [330].

Besides blocking HMGB1, the inhibition of other DAMPs can be assumed to have a beneficial effect on acute liver injury. For example, as briefly touched above, in studies on the model of APAP overdose, blockade of histones by anti-histone Abs was demonstrated to be protective [337, 339].

**9.9.3.3 Administration of SAMPs in Acute Organ Injuries**

The theoretical background of administering SAMPs in acute organ injuries is grounded on their ability to regulate host innate immune host responses, such as inhibiting the production of proinflammatory cytokines, stopping recruitment of neutrophils in inflammatory tissues, and stimulating polarization of M2-like macrophages to promote phagocytosis of apoptotic cells (efferocytosis) and cellular debris (compare Sect. 5.3.3). In other words, these properties of SAMPs could be therapeutically harnessed to prevent DAMP-promoted dyshomeostatic progression of inflammation that may result in acute and/or chronic organ dysfunction or even failure.

**Protective Effect of SAMPs on Traumatic Brain Injury**

Excitingly, a study on a model of TBI in mice (mentioned above [82]) provided initial evidence for SAMPs to mitigate the neuroinflammatory response following acute brain injury. One SAMP, the SPM RvD1, showed significant efficacy in ameliorating the motor and cognitive deficits resulting from diffuse TBI. The other SAMP, RvE1, elicited a dramatic increase in posttraumatic sleep and tempered microglia activation without significantly influencing behavioral outcome compared to saline treatment.
The divergence in histological (microglial activation) and physiological (sleep activity) outcomes from functional (motor and cognitive performance) outcomes was interpreted by the investigators in suggesting that microglial reactivity may contribute to posttraumatic sleep and that RvD1 may achieve therapeutic efficacy through means other than inflammation resolution alone. Given their observations, the authors argued [82] that SPMs demonstrate proof of principle as a therapeutic approach for diffuse brain injury, where additional studies are warranted.

In other lines of studies on a model of focal brain injury, RvD1 was observed to halt remote neuroinflammation and improve functional recovery after focal brain damage via ALX/FPR2 receptor-regulated miRNAs [453]. In these experiments, the in vivo administration of RvD1 promoted functional recovery and neuroprotection by reducing the activation of microglia and astrocytes as well as by impairing inflammatory-induced neuronal cell death in remote regions. In view of their findings, the authors proposed “that innovative therapies based on RvD1-ALX/FPR2 axis could be exploited to curtail remote damage and enable neuroprotective effects after acute focal brain damage.”

Protective Effect of SAMPs on Acute Lung Injury and Acute Respiratory Distress Syndrome

Initial studies on a potential beneficial effect of SAMPs administration on ALI and ARDS have also been reported. For example, inhibition of adenosine kinase, an enzyme that is known to inhibit elevated levels of the SAMP extracellular adenosine, was demonstrated to reduce the inflammatory changes associated with lung injury [167]. The therapeutic effect of active inhibition of adenosine kinase is interpreted as a consequence of increased adenosine levels, that is, a finding that indirectly reflects a protective effect of extracellular adenosine on ALI.

Earlier studies have already demonstrated that SPMs (i.e., LxA4, RvD1) can regulate the clearance of alveolar fluids in ARDS to protect the lung function [161–163]. Specifically, intravenous administration of RvD1 was demonstrated to stimulate clearance of alveolar fluid clearance through a mechanism partly depending on alveolar epithelial sodium channel and Na, K-ATPase activation via the FPR2 (also called ALX) → cAMP → PI3K signaling pathway [163]. Also, in other sets of experiments on a rat model of IRI-induced ALI [454], administration of the active N-terminal peptide of AnxA1 was shown to attenuate increased lung edema, neutrophil infiltration, inflammatory cytokine production, oxidative stress, and tissue damage. These improvements were shown to be attributed to FPR activation (for AnxA1, FPR2, and cAMP in SAMP-triggered resolution pathways, also compare Vol. 1 [1], Part IV, Sects. 14.4.2 and 14.4.3 and Fig. 14.5).

These promising experimental findings prompted Wang et al. [164] to write a review on this topic. The authors concluded: “The present review discusses a novel mechanism for pulmonary edema fluid reabsorption. SPMs might provide new opportunities to design “reabsorption-targeted” therapies with high degrees of precision in controlling ALI/ARDS.”
Protective Effect of SAMPs on Acute Liver Injury
There are also first clues to a protective role of SAMPs in acute liver injury. As already mentioned above, preclinical and clinical evidence suggesting SPMs being able to enhance nonalcoholic steatohepatitis and fibrosis resolution has already recently been reviewed [374]. Moreover, in studies on a model of nonalcoholic steatohepatitis in mice [347], hepatic AnxA1 was observed to be increased in parallel with progression of liver injury. In extension of this experiment, in vitro addition of recombinant AnxA1 to macrophages isolated from nonalcoholic steatohepatitis livers were found to downmodulate M1 polarization through stimulation of IL-10 production. Furthermore, the investigators could demonstrate that the degree of hepatic fibrosis was enhanced in methionine–choline-deficient-fed AnxA1KO mice. Given their observations [347], the authors concluded that macrophage-derived AnxA1 plays a functional role in modulating hepatic inflammation and fibrogenesis during progression of nonalcoholic steatohepatitis.

9.9.3.4 Concluding Remarks
Together, as reflected by some selected examples from the literature as addressed here, the preclinical evidence for the efficacy of targeting DAMPs in organ-specific injuries is convincing. Therefore, time appears to be mature to develop, design, and test DAMP-specific antagonists in these acute diseases to explore whether or not blocking DAMPs will benefit patients. Further, there is initial evidence for the successful use of SAMPs, in particular, SPMs as therapeutics to be administered in acute organ injuries. Thus, it can be cautiously assumed that first clinical trials in this exciting field of new therapeutic options will be reported soon.

9.9.4 Résumé
According to the reports quoted in this chapter, one can conceivably assume that DAMPs, fewer SAMPs (?) will soon find their way into clinical routine as diagnostic, prognostic, and predictive biomarkers in injury-induced organ diseases. However, as already discussed for polytrauma (Sect. 8.4.5), much more different, that is, more difficult to assess is their future routine use as therapeutic targets and therapeutics in solid organ injuries. Undoubtedly, treatment modalities based on inhibitors/antagonists, specifically targeting DAMPs, have provided encouraging results in several preclinical models of injury-induced inflammatory responses. However, before starting such trials, the possible risks of future therapeutic exploitation of DAMPs and SAMPs have to be clearly defined, as outlined in detail in Sect. 8.4.5. Nevertheless, as typical for current therapeutic achievements in medicine, clinical trials will give us the final answer to all these imponderabilities—in case they will be designed and conducted at all.
9.10 Outlook and Future Perspectives

This chapter should reflect the emerging role of DAMPs and SAMPs in injury-induced organ-specific diseases. In particular, the impact of DAMPs on promotion of organ-specific hyperinflammation, chronic nonresolving inflammation, and fibrosis, as well as the potential properties of SAMPs in resolving organ-specific inflammation are highlighted. To understand these complex scenarios, one may reduce the various cellular and molecular pathways involved to a fundamental sequence of injury-induced events. The “pathogenetic matrix” of such events—that could also be applied to other organ injuries not mentioned here—can be designed in the form of two axes (Fig. 9.5): acute or chronic organ injury → RCD → emission of DAMPs and SAMPs → necroinflammation → resolution of inflammation (restitutio ad integrum), or nonresolving hyperinflammation (acute organ failure), or nonresolving chronic inflammation transitioning to progressive fibrosis (chronic organ failure).

Regarding a final evaluation of the weight of using DAMPs and SAMPs as biomarkers, therapeutic targets, and therapeutics in injury-induced, organ-specific diseases, one has to wait for robust real-world data provided by future well-targeted clinical trials. It will be essential to design and conduct such studies under combination of molecular and clinical methods to ensure a high probability of reliable information that will enable safe decision-making in day-to-day clinical practice in the future.

Fig. 9.5 Model of a fundamental pathogenetic matrix of a sequence of acute or chronic organ injury-induced cellular/molecular pathways as generally observed in acute or chronic organ-specific diseases resulting in acute or chronic organ failure.
References

1. Land WG. Damage-associated molecular patterns in human diseases; Vol. 1: Injury-induced innate immune responses. Cham: Springer International Publishing AG; 2018. https://www.springer.com/de/book/9783319786544.

2. Blennow K, Brody DL, Kochanek PM, Levin H, McKee A, Ribbers GM, et al. Traumatic brain injuries. Nat Rev Dis Primers. 2016;2:16084. http://www.ncbi.nlm.nih.gov/pubmed/27853132.

3. Mayer AR, Quinn DK, Master CL. The spectrum of mild traumatic brain injury. Neurology. 2017;89:623–32. http://www.ncbi.nlm.nih.gov/pubmed/28701496.

4. Galgano M, Toshkezi G, Qiu X, Russell T, Chin L, Zhao L-R. Traumatic brain injury. Cell Transplant. 2017;26:1118–30. http://www.ncbi.nlm.nih.gov/pubmed/28933211.

5. Braun M, Vaibhav K, Saad NM, Fatima S, Vender JR, Baban B, et al. White matter damage after traumatic brain injury: a role for damage associated molecular patterns. Biochim Biophys Acta - Mol Basis Dis. 1863;2017:2614–26. http://www.ncbi.nlm.nih.gov/pubmed/28533056.

6. Sun M, McDonald SJ, Brady RD, O’Brien TJ, Shultz SR. The influence of immunological stressors on traumatic brain injury. Brain Behav Immun. 2018;69:618–28. http://www.ncbi.nlm.nih.gov/pubmed/29355823.

7. Stoica BA, Faden AL. Cell death mechanisms and modulation in traumatic brain injury. Neurotherapeutics. 2010;7:3–12. http://www.ncbi.nlm.nih.gov/pubmed/2129492.

8. Liu T, Zhao D, Cui H, Chen L, Bao Y, Wang Y, et al. Therapeutic hypothermia attenuates tissue damage and cytokine expression after traumatic brain injury by inhibiting necroptosis in the rat. Sci Rep. 2016;6:24547. http://www.ncbi.nlm.nih.gov/pubmed/27080932.

9. Liu Z-M, Chen Q-X, Chen Z-B, Tian D-F, Li M-C, Wang J-M, et al. RIP3 deficiency protects against traumatic brain injury (TBI) through suppressing oxidative stress, inflammation and apoptosis: dependent on AMPK pathway. Biochem Biophys Res Commun. 2018;499:112–9. http://linkinghub.elsevier.com/retrieve/pii/S0006291X18303875.

10. Zhang H-B, Cheng S-X, Tu Y, Zhang S, Hou S-K, Yang Z. Protective effect of mild-induced hypothermia against moderate traumatic brain injury in rats involved in necroptotic and apoptotic pathways. Brain Inj. 2017;31:406–15. http://www.ncbi.nlm.nih.gov/pubmed/28140659.

11. Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell. 2017;171:273–85. http://www.ncbi.nlm.nih.gov/pubmed/28985560.

12. Ji J, Kline AE, Amoscato A, Samhan-Arias AK, Sparvero LJ, Tyurin VA, et al. Lipidomics identifies cardiolipin oxidation as a mitochondrial target for redox therapy of brain injury. Nat Neurosci. 2012;15:1407–13. http://www.nature.com/articles/nn.3195.

13. Anthonymuthu TS, Kenny EM, Lamade AM, Kagan VE, Bayir H. Oxidized phospholipid signaling in traumatic brain injury. Free Radic Biol Med. 2018;124:493–503. https://linkinghub.elsevier.com/retrieve/pii/S0891584918311420.

14. Xie B, Wang Y, Lin Y, Mao Q, Feng J, Gao G, et al. Inhibition of ferroptosis attenuates tissue damage and improves long-term outcomes after traumatic brain injury in mice. CNS Neurosci Ther. 2019;25:465–75. http://www.ncbi.nlm.nih.gov/pubmed/30264934.

15. Magtanong L, Dixon SJ. Ferroptosis and brain injury. Dev Neurosci. 2018;40:382–95. http://www.ncbi.nlm.nih.gov/pubmed/30820017.

16. Adamczak SE, de Rivera Vaccari JP, Dale G, Brand FJ, Nonner D, Bullock MR, et al. Pyroptotic neuronal cell death mediated by the AIM2 inflammasome. J Cereb Blood Flow Metab. 2014;34:621–9. http://journals.sagepub.com/doi/10.1038/jcbfm.2013.236.

17. Lee SW, de Rivera Vaccari JP, Truettner JS, Dietrich WD, Keane RW. The role of microglial inflammasome activation in pyroptotic cell death following penetrating traumatic brain injury. J Neuroinflammation. 2019;16:27. https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-019-1423-6.

18. Hickey RW, Adelson PD, Johnnides MJ, Davis DS, Yu Z, Rose ME, et al. Cyclooxygenase-2 activity following traumatic brain injury in the developing rat. Pediatr Res. 2007;62:271–6. http://www.nature.com/doifinder/10.1203/PDR.0b013e3180db2902.
19. Zhang L, Zhang W-P, Hu H, Wang M-L, Sheng W-W, Yao H-T, et al. Expression patterns of 5-lipoxygenase in human brain with traumatic injury and astrocytoma. Neuropathology. 2006;26:99–106. http://www.ncbi.nlm.nih.gov/pubmed/16708542.

20. Harris LK, Black RT, Golden KM, Reeves TM, Povlishock JT, Phillips LL. Traumatic brain injury-induced changes in gene expression and functional activity of mitochondrial cytochrome C oxidase. J Neurotrauma. 2001;18:993–1009. http://www.liebertpub.com/doi/10.1089/08977150152693692.

21. Wenzel SE, Tyurina YY, Zhao J, St Croix CM, Dar HH, Mao G, et al. PEBP1 Wardens Ferroptosis by enabling lipoxygenase generation of lipid death signals. Cell. 2017;171:628–641.e26. https://linkinghub.elsevier.com/retrieve/pii/S0092867417311388.

22. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008;7:728–41. https://linkinghub.elsevier.com/retrieve/pii/S147442208701649.

23. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth. 2007;99:4–9. http://www.ncbi.nlm.nih.gov/pubmed/17573392.

24. Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. Dis Model Mech. 2013;6:1307–15. http://dmm.biologists.org/cgi/doi/10.1242/dmm.011585.

25. Quilliman N, Herson PS, Traystman RJ. Neuropathophysiology of brain injury. Anesthesiol Clin. 2016;34:453–64. http://www.ncbi.nlm.nih.gov/pubmed/27521191.

26. Simon DW, McGeachy MJ, Bayr H, Clark RSB, Koehaneck PM. The far-reaching scope of neuroinflammation after traumatic brain injury. Nat Rev Neurol. 2017;13:171–91. http://www.ncbi.nlm.nih.gov/pubmed/28186177.

27. Jassam YN, Izzy S, Whalen M, McGavern DB, El Khoury J. Neuroimmunology of traumatic brain injury: time for a paradigm shift. Neuron. 2017;95:1246–65. http://linkinghub.elsevier.com/retrieve/pii/S0896627317306128.

28. O’leary RA, Nichol AD. Pathophysiology of severe traumatic brain injury overview. J Neurosurg Sci. 2018;62:542–8. http://www.ncbi.nlm.nih.gov/pubmed/29790727.

29. Shi K, Zhang J, Dong J-F, Shi F-D. Dissemination of brain inflammation in traumatic brain injury. Cell Mol Immunol. 2019;16:523–30. http://www.nature.com/articles/s41423-019-0213-5.

30. Khatri N, Thakur M, Pareek V, Kumar S, Sharma S, Datusalia AK. Oxidative stress: major threat in traumatic brain injury. CNS Neurol Disord Drug Targets. 2018;17:689–95. http://www.eurekaselect.com/163257/article.

31. Shi H, Hua X, Kong D, Stein D, Hua F. Role of Toll-like receptor mediated signaling in traumatic brain injury. Neuropharmacology. 2019;145:259–67. https://linkinghub.elsevier.com/retrieve/pii/S0028390818304003.

32. Puntambekar SS, Saber M, Lamb BT, Kokiko-Cochran ON. Cellular players that shape evolving pathology and neurodegeneration following traumatic brain injury. Brain Behav Immun. 2018;71:9–17. http://www.ncbi.nlm.nih.gov/pubmed/29601944.

33. Stocchetti N, Maas AIR. Traumatic intracranial hypertension. N Engl J Med. 2014;370:2121–30. http://www.ncbi.nlm.nih.gov/pubmed/24869722.

34. Winkler EA, Minter D, Yue JK, Manley GT. Cerebral edema in traumatic brain injury. Neurosurg Clin N Am. 2016;27:473–88. http://www.ncbi.nlm.nih.gov/pubmed/27637397.

35. Jha RM, Kocheaneck PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. Neuropharmacology. 2019;145:230–46. http://www.ncbi.nlm.nih.gov/pubmed/30086289.

36. Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. Trends Immunol. 2007;28:138–45. https://linkinghub.elsevier.com/retrieve/pii/S1471490607000245.
38. Rivest S. Regulation of innate immune responses in the brain. Nat Rev Immunol. 2009;9:429–39. http://www.ncbi.nlm.nih.gov/pubmed/19461673.
39. Lehhardt S. Innate immunity and neuroinflammation in the CNS: the role of microglia in Toll-like receptor-mediated neuronal injury. Glia. 2010;58:253–63. http://doi.wiley.com/10.1002/glia.20928.
40. Liesz A, Dalpke A, Mracsko E, Antoine DJ, Roth S, Zhou W, et al. DAMP signaling is a key pathway inducing immune modulation after brain injury. J Neurosci. 2015;35:583–98. http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.2439-14.2015.
41. Kelley KW, Dantzer R. Alcoholism and inflammation: neuroimmunology of behavioral and mood disorders. Brain Behav Immun. 2011;25:S13–20. https://linkinghub.elsevier.com/retrieve/pii/S0889159110005866.
42. Orio L, Alen F, Pavón FJ, Serrano A, García-Bueno B. Oleoylthanolamide, neuroinflammation, and alcohol abuse. Front Mol Neurosci. 2019;11:490. http://www.ncbi.nlm.nih.gov/pubmed/30687006.
43. Obernier JA, Bouldin TW, Crews FT. Binge ethanol exposure in adult rats causes necrotic cell death. Alcohol Clin Exp Res. 2002;26:547–57. http://www.ncbi.nlm.nih.gov/pubmed/11981132.
44. de la Monte SM, Kril JJ. Human alcohol-related neuropathology. Acta Neuropathol. 2014;127:71–90. http://www.ncbi.nlm.nih.gov/pubmed/24370929.
45. Charmess ME. Brain lesions in alcoholics. Alcohol Clin Exp Res. 1993;17:2–11. http://www.ncbi.nlm.nih.gov/pubmed/8452204.
46. Victor M. Alcoholic dementia. Can J Neurol Sci. 1994;21:88–99. http://www.ncbi.nlm.nih.gov/pubmed/8087744.
47. Osna NA, Kharbanda KK. Multi-organ alcohol-related damage: mechanisms and treatment. Biomolecules. 2016;6:20. http://www.mdpi.com/2218-273X/6/2/20.
48. Souza-Smith FM, Lang CH, Nagy LE, Bailey SM, Parsons LH, Murray GJ. Physiological processes underlying organ injury in alcohol abuse. Am J Physiol Metab. 2016;311:E605–19. http://www.ncbi.nlm.nih.gov/pubmed/27436613.
49. Yang L, Guo Y, Wen D, Yang L, Chen Y, Zhang G, et al. Bone fracture enhances trauma brain injury. Scand J Immunol. 2016;83:26–32. http://www.ncbi.nlm.nih.gov/pubmed/26448486.
50. Corps KN, Roth TL, McGavern DB. Inflammation and neuroprotection in traumatic brain injury. JAMA Neurol. 2015;72:355–62. http://archneur.jamanetwork.com/article.aspx?doi=10.1001/jamaneurol.2014.3558.
51. Sheikh AM, Nagai A, Ryu JK, McLarnon JG, Kim SU, Masuda J. Lyosphosphatidylcholine induces glial cell activation: role of rho kinase. Glia. 2009;57:898–907. http://doi.wiley.com/10.1002/glia.20815.
52. Uchida K. Redox-derived damage-associated molecular patterns: ligand function of lipid peroxidation adducts. Redox Biol. 2013;1:94–6. http://linkinghub.elsevier.com/retrieve/pii/S2213231712000201.
53. Ransohoff RM, Brown MA. Innate immunity in the central nervous system. J Clin Invest. 2012;122:1164–71. http://www.jci.org/articles/view/58644.
54. Ziebell JM, Morganti-Kossmann MC. Involvement of pro- and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. Neurotherapeutics. 2010;7:22–30. http://link.springer.com/10.1016/j.nurt.2009.10.016.
55. Parker TM, Nguyen AH, Rabang JR, Patil A-A, Agrawal DK. The danger zone: systematic review of the role of HMGB1 danger signalling in traumatic brain injury. Brain Inj. 2017;31:2–8. http://www.ncbi.nlm.nih.gov/pubmed/27819487.
56. Okuma Y, Liu K, Wake H, Zhang J, Maruo T, Date I, et al. Anti-high mobility group box-1 antibody therapy for traumatic brain injury. Ann Neurol. 2012;72:373–84. http://doi.wiley.com/10.1002/ana.23602.
57. Gao T-L, Yuan X-T, Yang D, Dai H-L, Wang W-J, Peng X, et al. Expression of HMGB1 and RAGE in rat and human brains after traumatic brain injury. J Trauma Acute Care Surg. 2012;72:643–9. https://insights.ovid.com/crossref?an=01586154-201203000-00014.
58. Su X, Wang H, Zhao J, Pan H, Mao L. Beneficial effects of ethyl pyruvate through inhibiting high-mobility group box 1 expression and TLR4/NF-κB pathway after traumatic brain injury in the rat. Mediators Inflamm. 2011;2011:807142. http://www.hindawi.com/journals/mi/2011/807142/.

59. Laird MD, Shields JS, Sukumari-Ramesh S, Kimber DE, Fessler RD, Shakir B, et al. High mobility group box protein-1 promotes cerebral edema after traumatic brain injury via activation of toll-like receptor 4. Glia. 2014;62:26–38. http://doi.wiley.com/10.1002/glia.22581.

60. Gu X-J, Xu J, Ma B-Y, Chen G, Gu P-Y, Wei D, et al. Effect of glycyrrhizin on traumatic brain injury in rats and its mechanism. Chin J Traumatol. 2014;17:1–7. http://www.ncbi.nlm.nih.gov/pubmed/24506915.

61. Okuma Y, Liu K, Wake H, Liu R, Nishimura Y, Hui Z, et al. Glycyrrhizin inhibits traumatic brain injury by reducing HMGB1-RAGE interaction. Neuropharmacology. 2014;85:18–26. http://linkinghub.elsevier.com/retrieve/pii/S0028390814001749.

62. Szabo G, Lippai D. Converging actions of alcohol on liver and brain immune signaling. Int Rev Neurobiol. 2014;118:359–80. https://linkinghub.elsevier.com/retrieve/pii/B9780128012840000117.

63. Vetreno RP, Crews FT. Adolescent binge drinking increases expression of the danger signal receptor agonist HMGB1 and Toll-like receptors in the adult prefrontal cortex. Neuroscience. 2012;226:475–88. https://linkinghub.elsevier.com/retrieve/pii/S0306452212008809.

64. Crews FT, Qin L, Sheedy D, Vetreno RP, Zou J. High mobility group box 1/Toll-like receptor danger signaling increases brain neuroimmune activation in alcohol dependence. Biol Psychiatry. 2013;73:602–12. https://linkinghub.elsevier.com/retrieve/pii/S000632231200889X.

65. Wang X, Chu G, Yang Z, Sun Y, Zhou H, Li M, et al. Ethanol directly induced HMGB1 release through NOX2/NLRP1 inflammasome in neuronal cells. Toxicology. 2015;334:104–10. http://www.ncbi.nlm.nih.gov/pubmed/26079697.

66. Wang K-Y, Yu G-F, Zhang Z-Y, Huang Q, Dong X-Q. Plasma high-mobility group box 1 levels and prediction of outcome in patients with traumatic brain injury. Clin Chim Acta. 2012;413:1737–41. http://linkinghub.elsevier.com/retrieve/pii/S0009898112003415.

67. Au AK, Aneja RK, Bell MJ, Bayir H, Feldman K, Adelson PD, et al. Cerebrospinal fluid levels of high-mobility group box 1 and cytochrome C predict outcome after pediatric traumatic brain injury. J Neurotrauma. 2012;29:2013–21. http://www.liebertpub.com/doi/10.1089/neu.2011.1217.

68. Antón M, Rodríguez-González A, Rodríguez-Rojo IC, Pastor A, Correas Á, Serrano A, et al. Increased plasma oleoylethanolamide and palmitoleoyl ethanolamide levels correlate with inflammatory changes in alcohol binge drinkers: the case of HMGB1 in women. Addict Biol. 2018;23:1242–50. http://doi.wiley.com/10.1111/adb.12580.

69. Vetreno RP, Qin L, Crews FT. Increased receptor for advanced glycation end product expression in the human alcoholic prefrontal cortex is linked to adolescent drinking. Neurobiol Dis. 2013;59:52–62. https://linkinghub.elsevier.com/retrieve/pii/S0969996113001964.

70. Walko TD, Bola RA, Hong JD, Au AK, Bell MJ, Koachane P, et al. Cerebrospinal fluid mitochondrial DNA: a novel DAMP in pediatric traumatic brain injury. Shock. 2014;41:499–503. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00024382-201406000-00005.

71. Ingebrigtsen T, Romner B, Kongstad P, Langbakk B. Increased serum concentrations of protein S-100 after minor head injury: a biochemical serum marker with prognostic value? J Neurol Neurosurg Psychiatry. 1995;59:103–4. http://www.ncbi.nlm.nih.gov/pubmed/7608699.

72. Vos PE, Jacobs B, Andriessen TMJ, Lamers KJB, Borm GF, Beems T, et al. GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology. 2010;75:1786–93. http://www.neurology.org/cgi/doi/10.1212/WNL.0b013e3181fd62d2.

73. Thelin EP, Nelson DW, Bellander B-M. A review of the clinical utility of serum S100B protein levels in the assessment of traumatic brain injury. Acta Neurochir. 2017;159:209–25. http://www.ncbi.nlm.nih.gov/pubmed/27957604.
74. Park S-H, Hwang S-K. Prognostic value of serum levels of S100 calcium-binding protein B, neuron-specific enolase, and interleukin-6 in pediatric patients with traumatic brain injury. World Neurosurg. 2018;118:e534–42. http://www.ncbi.nlm.nih.gov/pubmed/30257306.

75. Bayir H, Marion DW, Puccio AM, Wisniewski SR, Janesko KL, Clark RSB, et al. Marked gender effect on lipid peroxidation after severe traumatic brain injury in adult patients. J Neurotrauma. 2004;21:1–8. http://www.liebertpub.com/doi/10.1089/089771504772695896.

76. Cristofori L, Tavazzi B, Gambin R, Vagnozzi R, Signoretti S, Amorini AM, et al. Biochemical analysis of the cerebrospinal fluid: evidence for catastrophic energy failure and oxidative damage preceding brain death in severe head injury: a case report. Clin Biochem. 2005;38:97–100. http://linkinghub.elsevier.com/retrieve/pii/S0009912004002516.

77. Lorente L, Martín MM, Abreu-González P, Ramos L, Argueso M, Cáceres JJ, et al. Association between serum malondialdehyde levels and mortality in patients with severe brain trauma injury. J Neurotrauma. 2015;32:1–6. http://www.ncbi.nlm.nih.gov/pubmed/25054973.

78. Kagan VE, Mao G, Qu F, Angeli JPF, Doll S, Croix CS, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol. 2017;13:81–90. http://www.nature.com/articles/nchembio.2238.

79. Orrenius S, Zhivotovsky B. Cardiolipin oxidation sets cytochrome C free. Nat Chem Biol. 2005;1:188–9. http://www.nature.com/doifinder/10.1038/nchembio0905-188.

80. Kagan VE, Tyurin VA, Jiang J, Tyurina YY, Ritov VB, Amoscat AA, et al. Cytochrome C acts as a cardiolipin oxygenase required for release of proapoptotic factors. Nat Chem Biol. 2005;1:223–32. http://www.nature.com/doifinder/10.1038/nchembio727.

81. Bayir H, Tyurin VA, Tyurina YY, Viner R, Ritov V, Amoscat AA, et al. Selective early cardiolipin peroxidation after traumatic brain injury: an oxidative lipidomics analysis. Ann Neurol. 2007;62:154–69. http://doi.wiley.com/10.1002/ana.21168.

82. Harrison JL, Rowe RK, Ellis TW, Yee NS, O’Hara BF, Adelson PD, et al. Resolvins AT-D1 and E1 differentially impact functional outcome, post-traumatic sleep, and microglial activation following diffuse brain injury in the mouse. Brain Behav Immun. 2015;47:131–40. http://www.ncbi.nlm.nih.gov/pubmed/25585137.

83. Jackson EK, Kotermanski SE, Menshikova EV, Dubey RK, Jackson TC, Kochanek PM. Adenosine production by brain cells. J Neurochem. 2017;141:676–93. http://www.ncbi.nlm.nih.gov/pubmed/28294336.

84. Robertson CL, Bell MJ, Kochanek PM, Adelson PD, Ruppel RA, Carcillo JA, et al. Increased adenosine in cerebrospinal fluid after severe traumatic brain injury in infants and children: association with severity of injury and excitotoxicity. Crit Care Med. 2001;29:2287–93. http://www.ncbi.nlm.nih.gov/pubmed/11801827.

85. Kochanek PM, Vagni VA, Janesko KL, Washington CB, Crumrine PK, Garman RH, et al. Adenosine A1 receptor knockout mice develop lethal status epilepticus after experimental traumatic brain injury. J Cereb Blood Flow Metab. 2006;26:565–75. http://www.ncbi.nlm.nih.gov/pubmed/16121125.

86. Haselkorn ML, Shellington DK, Jackson EK, Vagni VA, Janesko-Feldman K, Dubey RK, et al. Adenosine A1 receptor activation as a brake on the microglial response after experimental traumatic brain injury in mice. J Neurotrauma. 2010;27:901–10. http://www.ncbi.nlm.nih.gov/pubmed/20121416.

87. Kota DJ, Prabhakara KS, Toledano-Furman N, Bhattachar D, Chen Q, DiCarlo B, et al. Prostaglandin E2 indicates therapeutic efficacy of mesenchymal stem cells in experimental traumatic brain injury. Stem Cells. 2017;35:1416–30. http://www.ncbi.nlm.nih.gov/pubmed/28233425.

88. Wang Z, Chen Z, Yang J, Yang Z, Yin J, Zuo G, et al. Identification of two phosphorylation sites essential for annexin A1 in blood–brain barrier protection after experimental intracerebral hemorrhage in rats. J Cereb Blood Flow Metab. 2017;37:2509–25. http://www.ncbi.nlm.nih.gov/pubmed/27634935.

89. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet (London, England). 1967;2:319–23. http://www.ncbi.nlm.nih.gov/pubmed/4143721.
90. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Invest. 2012;122:2731–40. http://www.ncbi.nlm.nih.gov/pubmed/22850883.

91. Johnson ER, Matthay MA. Acute lung injury: epidemiology, pathogenesis, and treatment. J Aerosol Med Pulm Drug Deliv. 2010;23:243–52. http://www.ncbi.nlm.nih.gov/pubmed/20073554.

92. Butt Y, Kurdowska A, Allen TC. Acute lung injury: a clinical and molecular review. Arch Pathol Lab Med. 2016 [cited 2019 Sep 14];140:345–50. http://www.ncbi.nlm.nih.gov/pubmed/27028393.

93. Komiya K, Akaba T, Kozaki Y, Kadota J-I, Rubin BK. A systematic review of diagnostic methods to differentiate acute lung injury/acute respiratory distress syndrome from cardiogenic pulmonary edema. Crit Care. 2017;21:228. http://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1809-8.

94. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315:788–800. http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.0291.

95. Rawal G, Yadav S, Kumar R. Acute respiratory distress syndrome: an update and review. J Transl Intern Med. 2018;6:74–7. http://www.ncbi.nlm.nih.gov/pubmed/29984201.

96. Confalonieri M, Salton F, Fabiano F. Acute respiratory distress syndrome. Eur Respir Rev. 2017;26:160116. http://err.ersjournals.com/lookup/doi/10.1183/16000617.0116-2016.

97. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526–33. http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.5669.

98. Matute-Bello G, Liles WC, Steinberg KP, Kiener PA, Mongovin S, Chi EY, et al. Soluble Fas ligand induces epithelial cell apoptosis in humans with acute lung injury (ARDS). J Immunol. 1999;163:2217–25. http://www.ncbi.nlm.nih.gov/pubmed/10438964.

99. Chambers E, Rounds S, Lu Q. Pulmonary endothelial cell apoptosis in emphysema and acute lung injury. Adv Anat Embryol Cell Biol. 2018;228:63–86. http://www.ncbi.nlm.nih.gov/pubmed/29288386.

100. Wang L, Wang T, Li H, Liu Q, Zhang Z, Xie W, et al. Receptor interacting protein 3-mediated necroptosis promotes lipopolysaccharide-induced inflammation and acute respiratory distress syndrome in mice. Ahmad S, editor. PLoS One. 2016;11:e0155723. http://www.ncbi.nlm.nih.gov/pubmed/27195494.

101. Pan L, Yao D-C, Yu Y-Z, Chen B-J, Li S-J, Hu G-H, et al. Activation of necroptosis in a rat model of acute respiratory distress syndrome induced by oleic acid. Sheng Li Xue Bao. 2016;68:661–8. http://www.ncbi.nlm.nih.gov/pubmed/27778032.

102. Qing DY, Conegliano D, Shashaty MGS, Seo J, Reilly JP, Worthen GS, et al. Red blood cells induce necroptosis of lung endothelial cells and increase susceptibility to lung inflammation. Am J Respir Crit Care Med. 2014;190:1243–54. http://www.atsjournals.org/doi/abs/10.1164/rccm.201406-1095OC.

103. Fan EKY, Fan J. Regulation of alveolar macrophage death in acute lung inflammation. Respir Rev. 2018;19:50. http://www.ncbi.nlm.nih.gov/pubmed/29587748.

104. Li H, Zhou X, Tan H, Hu Y, Zhang L, Liu S, et al. Neutrophil extracellular traps contribute to the pathogenesis of acid-aspiration-induced ALI/ARDS. Oncotarget. 2018;9:1772–84. http://www.ncbi.nlm.nih.gov/pubmed/29416730.

105. Bersten AD, Edibam C, Hunt T, Moran J, Australian and New Zealand Intensive Care Society Clinical Trials Group. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. Am J Respir Crit Care Med. 2002;165:443–8. http://www.ncbi.nlm.nih.gov/pubmed/11850334.

106. Epelbaum O, Aronow WS. Mechanical ventilation in the acute respiratory distress syndrome. Hosp Pract. 2017;45:88–98. http://www.ncbi.nlm.nih.gov/pubmed/28510501.

107. Lee K-Y. Pneumonia, acute respiratory distress syndrome, and early immune-modulator therapy. Int J Mol Sci. 2017;18:388. http://www.mdpi.com/1422-0067/18/2/388.
108. Yang C-Y, Chen C-S, Yang G-T, Cheng Y-L, Yong S-B, Wu M-Y, et al. New insights into the immune molecular regulation of the pathogenesis of acute respiratory distress syndrome. Int J Mol Sci. 2018;19:588. http://www.ncbi.nlm.nih.gov/pubmed/29462936.

109. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000;342:1334–49. http://www.nejm.org/doi/abs/10.1056/NEJM200005043421806.

110. Herold S, Mayer K, Lohmeyer J. Acute lung injury: how macrophages orchestrate resolution of inflammation and tissue repair. Front Immunol. 2011;2:65. http://journal.frontiersin.org/article/10.3389/fimmu.2011.00065/abstract.

111. Matthay MA, Ware LB. Resolution of alveolar edema in acute respiratory distress syndrome. Physiology and biology. Am J Respir Crit Care Med. 2015;192:124–5. http://www.ncbi.nlm.nih.gov/pubmed/26177166.

112. Aggarwal NR, King LS, D’Alessio FR. Diverse macrophage populations mediate acute lung inflammation and resolution. Am J Physiol Cell Mol Physiol. 2014;306:L709–25. http://www.ncbi.nlm.nih.gov/pubmed/24508730.

113. Robb CT, Regan KH, Dorward DA, Rossi AG. Key mechanisms governing resolution of lung inflammation. Semin Immunopathol. 2016;38:425–48. http://www.ncbi.nlm.nih.gov/pubmed/27116944.

114. Matthay MA, Zemans RL. The acute respiratory distress syndrome: pathogenesis and treatment. Annu Rev Pathol. 2011;6:147–63. http://www.annualreviews.org/doi/10.1146/annurev-pathol-011110-130158.

115. Katzenstein A-L. Acute lung injury patterns: diffuse alveolar damage and bronchiolitis obliterans organizing pneumonia. In: Katzenstein A-L, editor. Katzenstein and Askin’s surgical pathology of non-neoplastic lung disease. Philadelphia: Elsevier Saunders; 2006, ISBN-13:978-0721600413.

116. Tolle LB, Standiford TJ. Danger-associated molecular patterns (DAMPs) in acute lung injury. J Pathol. 2013;229:145–56. http://www.ncbi.nlm.nih.gov/pubmed/23097158.

117. Englert JA, Bobba C, Baron RM. Integrating molecular pathogenesis and clinical translation in sepsis-induced acute respiratory distress syndrome. JCI Insight. 2019;4(2):e124061. http://www.ncbi.nlm.nih.gov/pubmed/30674720.

118. Land WG. Transfusion-related acute lung injury: the work of DAMPs. Transfus Med Hemother. 2013;40:3–13. https://www.karger.com/Article/FullText/345688.

119. Simmons JD, Lee Y-LL, Pastukh VM, Capley G, Muscat CA, Muscat DC, et al. Potential contribution of mitochondrial DNA damage associated molecular patterns in transfusion products to the development of acute respiratory distress syndrome after multiple transfusions. J Trauma Acute Care Surg. 2017;82:1023–9. http://insights.ovid.com/crossref?an=01586154-201706000-00007.

120. Gan L, Chen X, Sun T, Li Q, Zhang R, Zhang J, et al. Significance of serum mtDNA concentration in lung injury induced by hip fracture. Shock. 2015;44:52–7. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00024382-201507000-00008.

121. Kang J-W, Kim S-J, Cho H-I, Lee S-M. DAMPs activating innate immune responses in sepsis. Ageing Res Rev. 2015;24:54–65. https://linkinghub.elsevier.com/retrieve/pii/S1568163715000318.

122. Ueno T, Ikeda T, Ikeda K, Taniuchi H, Suda S, Yeung MY, et al. HMGB-1 as a useful prognostic biomarker in sepsis-induced organ failure in patients undergoing PMX-DHP. J Surg Res. 2011;171:183–90. https://linkinghub.elsevier.com/retrieve/pii/S0022480409012669.

123. Patel MC, Shirey KA, Boukhvalova MS, Vogel SN, Blanco JCG. Serum high-mobility-group box 1 as a biomarker and a therapeutic target during respiratory virus infections. Sher A, editor. MBio. 2018;9(2):e00246-18. http://mbio.asm.org/lookup/doi/10.1128/mBio.00246-18.

124. Abraham E, Arcaroli J, Carmody A, Wang H, Tracey KJ. HMGB-1 as a mediator of acute lung inflammation. J Immunol. 2000;165:2950–4. http://www.ncbi.nlm.nih.gov/pubmed/10975801.

125. Ren D, Sun R, Wang S. Role of inducible nitric oxide synthase expressed by alveolar macrophages in high mobility group box 1-induced acute lung injury. Inflamm Res. 2006;55:207–15. http://link.springer.com/10.1007/s00011-006-0072-2.
126. Kim JY, Park JS, Strassheim D, Douglas I, Diaz del Valle F, Asehnoune K, et al. HMGB1 contributes to the development of acute lung injury after hemorrhage. Am J Physiol Lung Cell Mol Physiol. 2005;288:L958–65. http://www.physiology.org/doi/10.1152/ajplung.00359.2004.

127. Entezari M, Javdan M, Antoine DJ, Morrow DMP, Sitapara RA, Patel V, et al. Inhibition of extracellular HMGB1 attenuates hyperoxia-induced inflammatory acute lung injury. Redox Biol. 2014;2:314–22. http://www.ncbi.nlm.nih.gov/pubmed/24563849.

128. Qin M-Z, Gu Q-H, Tao J, Song X-Y, Gan G-S, Luo Z-B, et al. Ketamine effect on HMGB1 and TLR4 expression in rats with acute lung injury. Int J Clin Exp Pathol. 2015;8:12943–8. http://www.ncbi.nlm.nih.gov/pubmed/26722488.

129. Liu X, Xu Q, Mei L, Lei H, Wen Q, Miao J, et al. Paeonol attenuates acute lung injury by inhibiting HMGB1 in lipopolysaccharide-induced shock rats. Int Immunopharmacol. 2018;61:169–77. http://www.ncbi.nlm.nih.gov/pubmed/29883962.

130. Ogawa EN, Ishizaka A, Tasaka S, Koh H, Ueno H, Amaya F, et al. Contribution of high-mobility group box 1 to the development of ventilator-induced lung injury. Am J Respir Crit Care Med. 2006;174:400–7. http://www.atsjournals.org/doi/abs/10.1164/rccm.200605-699OC.

131. Patel VS, Sitapara RA, Gore A, Phan B, Sharma L, Sampat V, et al. High mobility group box 1 mediates hyperoxia-induced impairment of Pseudomonas aeruginosa clearance and inflammatory lung injury in mice. Am J Respir Cell Mol Biol. 2013;48:280–7. http://www.atsjournals.org/doi/abs/10.1165/rcmb.2012-0279OC.

132. Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, et al. HMG-1 as a late mediator of endotoxin lethality in mice. Science. 1999;285:248–51. http://www.ncbi.nlm.nih.gov/pubmed/10398600.

133. Ueno H, Matsuda T, Hashimoto S, Amaya F, Kitamura Y, Tanaka M, et al. Contributions of high mobility group box protein in experimental and clinical acute lung injury. Am J Respir Crit Care Med. 2004;170:1310–6. http://www.atsjournals.org/doi/abs/10.1164/rccm.200402-188OC.

134. van Zoelen MAD, Ishizaka A, Wolthuls EK, Choi G, van der Poll T, Schultz MJ. Pulmonary levels of high-mobility group box 1 during mechanical ventilation and ventilator-associated pneumonia. Shock. 2008;29:441–5. http://insights.ovid.com/crossref?an=00024382-200804000-00003.

135. Tseng C-C, Fang W-F, Leung S-Y, Chen H-C, Chang Y-C, Wang C-C, et al. Impact of serum biomarkers and clinical factors on intensive care unit mortality and 6-month outcome in relatively healthy patients with severe pneumonia and acute respiratory distress syndrome. Dis Markers. 2014;2014:1–9. http://www.ncbi.nlm.nih.gov/pubmed/24723739.

136. Chase MA, Wheeler DS, Lierl KM, Hughes VS, Wong HR, Page K. Hsp72 induces inflammation and regulates cytokine production in airway epithelium through a TLR4- and NF-κappaB-dependent mechanism. J Immunol. 2007;179:6318–24. http://www.ncbi.nlm.nih.gov/pubmed/17947709.

137. Ganter MT, Ware LB, Howard M, Roux J, Gartland B, Matthay MA, et al. Extracellular heat shock protein 72 is a marker of the stress protein response in acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2006;291:L354–61. http://www.physiology.org/doi/10.1152/ajplung.00405.2005.

138. Sun S, Sursal T, Adibnia Y, Zhao C, Zheng Y, Li H, et al. Mitochondrial DAMPs increase endothelial permeability through neutrophil dependent and independent pathways. Zhao Y-Y, editor. PLoS One. 2013;8:e59989. http://www.ncbi.nlm.nih.gov/pubmed/23527291.

139. Kuck JL, Obiako BO, Gorodnya OM, Pastukh VM, Kua J, Simmons JD, et al. Mitochondrial DNA damage-associated molecular patterns mediate a feed-forward cycle of bacteria-induced vascular injury in perfused rat lungs. Am J Physiol Lung Cell Mol Physiol. 2015;308:L1078–85. http://www.physiology.org/doi/10.1152/ajplung.00015.2015.

140. Zhang L, Deng S, Zhao S, Ai Y, Zhang L, Pan P, et al. Intra-peritoneal administration of mitochondrial DNA provokes acute lung injury and systemic inflammation via Toll-like receptor 9. Int J Mol Sci. 2016;17:1425. http://www.mdpi.com/1422-0067/17/9/1425.

141. Lee Y-L, Obiako B, Gorodnya OM, Ruchko MV, Kuck JL, Pastukh VM, et al. Mitochondrial DNA damage initiates acute lung injury and multi-organ system failure evoked in rats by
intra-tracheal Pseudomonas aeruginosa. Shock. 2017;48:54–60. http://insights.ovid.com/crossref?an=00024382-201707000-00008.

142. Simmons JD, Freno DR, Muscat CA, Obiako B, Lee Y-LL, Pastukh VM, et al. Mitochondrial DNA damage associated molecular patterns in ventilator-associated pneumonia: prevention and reversal by intratracheal DNase I. J Trauma Acute Care Surg. 2017;82:120–5. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=01586154-201701000-00016.

143. Zhang X, Wang T, Yuan Z-C, Dai L-Q, Zeng N, Wang H, et al. Mitochondrial peptides cause proinflammatory responses in the alveolar epithelium via FPR-1, MAPKs, and AKT: a potential mechanism involved in acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2018;315:L775–86. https://www.physiology.org/doi/10.1152/ajplung.00466.2017.

144. Abrams ST, Zhang N, Manson J, Liu T, Dart C, Baluwa F, et al. Circulating histones are mediators of trauma-associated lung injury. Am J Respir Crit Care Med. 2013;187:160–9. http://www.atsjournals.org/doi/abs/10.1164/rccm.201206-1037OC.

145. Lv X, Wen T, Song J, Xie D, Wu L, Jiang X, et al. Extracellular histones are clinically relevant mediators in the pathogenesis of acute respiratory distress syndrome. Respir Res. 2017;18:165. http://www.ncbi.nlm.nih.gov/pubmed/28865478.

146. Lorenz E, Muhlebach MS, Tessier PA, Alexis NE, Duncan Hite R, Seeds MC, et al. Different expression ratio of S100A8/A9 and S100A12 in acute and chronic lung diseases. Respir Med. 2008;102:567–73. http://linkinghub.elsevier.com/retrieve/pii/S0954611107004714.

147. Chakraborty D, Zenker S, Rossaint J, Hölscher A, Pohlen M, Zarbock A, et al. Alarmin S100A8 activates alveolar epithelial cells in the context of acute lung injury in a TLR4-dependent manner. Front Immunol. 2017;8:1493. http://journal.frontiersin.org/article/10.3389/fimmu.2017.01493/full.

148. Hiroshima Y, Hsu K, Tedla N, Wang SW, Chow S, Kawaguchi N, et al. S100A8/A9 and S100A9 reduce acute lung injury. Immunol Cell Biol. 2017;95:461–72. http://www.ncbi.nlm.nih.gov/pubmed/28074060.

149. Copland IB, Kavanagh BP, Engelberts D, McKerlie C, Belik J, Post M. Early changes in lung gene expression due to high tidal volume. Am J Respir Crit Care Med. 2003;168:1051–9. http://www.atsjournals.org/doi/abs/10.1164/rccm.200208-964OC.

150. Altemeier WA, Matute-Bello G, Gharib SA, Glenny RW, Martin TR, Liles WC. Modulation of lipopolysaccharide-induced gene transcription and promotion of lung injury by mechanical ventilation. J Immunol. 2005;175:3369–76. http://www.ncbi.nlm.nih.gov/pubmed/16116230.

151. Wittkowski H, Sturrock A, van Zoelen MAD, Viemann D, van der Poll T, Hoidal JR, et al. Neutrophil-derived S100A12 in acute lung injury and respiratory distress syndrome. Crit Care Med. 2007;35:1369–75. https://insights.ovid.com/crossref?an=00003246-200705000-00024.

152. Feng Z, Qi S, Zhang Y, Qi Z, Yan L, Zhou J, et al. Ly6G+ neutrophil-derived miR-223 inhibits the NLRP3 inflammasome in mitochondrial DAMP-induced acute lung injury. Cell Death Dis. 2017;8:e3170. http://www.ncbi.nlm.nih.gov/pubmed/29144508.

153. Li D, Ren W, Jiang Z, Zhu L. Regulation of the NLRP3 inflammasome and macrophage pyroptosis by the p38 MAPK signaling pathway in a mouse model of acute lung injury. Mol Med Rep. 2018;18:4399–409. http://www.ncbi.nlm.nih.gov/pubmed/30152849.

154. Rich PB, Douillet CD, Mahler SA, Husain SA, Boucher RC. Adenosine triphosphate is released during injurious mechanical ventilation and contributes to lung edema. J Trauma. 2003;55:290–7. https://insights.ovid.com/crossref?an=00005373-200308000-00014.

155. Matsuyama H, Amaya F, Hashimoto S, Ueno H, Beppu S, Mizuta M, et al. Acute lung inflammation and ventilator-induced lung injury caused by ATP via the P2Y receptors: an experimental study. Respir Res. 2008;9:79. http://respiratory-research.biomedcentral.com/articles/10.1186/1465-9921-9-79.

156. Kuipers MT, Aslam H, Vlaar APJ, Juffermans NP, Tuip-de Boer AM, Hegeman MA, et al. Pre-treatment with allopurinol or uricase attenuates barrier dysfunction but not inflammation during murine ventilator-induced lung injury. Ryffel B, editor. PLoS One. 2012;7:e50559. https://dx.plos.org/10.1371/journal.pone.0050559.
157. Gasse P, Riteau N, Charron S, Girre S, Fick L, Pétrilli V, et al. Uric acid is a danger signal activating NALP3 inflammasome in lung injury inflammation and fibrosis. Am J Respir Crit Care Med. 2009;179:903–13. http://www.atsjournals.org/doi/abs/10.1164/rccm.200808-1274OC.

158. Esposito AJ, Bhatraju PK, Stapleton RD, Wurfel MM, Mikacenic C. Hyaluronic acid is associated with organ dysfunction in acute respiratory distress syndrome. Crit Care. 2017;21:304. http://www.ncbi.nlm.nih.gov/pubmed/29237497.

159. Schmidt EP, Overdier KH, Sun X, Lin L, Liu X, Yang Y, et al. Urinary glycosaminoglycans predict outcomes in septic shock and acute respiratory distress syndrome. Am J Respir Crit Care Med. 2016;194:439–49. http://www.atsjournals.org/doi/10.1164/rccm.201511-2281OC.

160. Levy BD, Serhan CN. Resolution of acute inflammation in the lung. Annu Rev Physiol. 2014;76:467–92. http://www.ncbi.nlm.nih.gov/pubmed/24313723.

161. Wang Q, Lian Q-Q, Li R, Ying B-Y, He Q, Chen F, et al. Lipoxin A(4) activates alveolar epithelial sodium channel, Na,K-ATPase, and increases alveolar fluid clearance. Am J Respir Cell Mol Biol. 2013;48:610–8. http://www.atsjournals.org/doi/abs/10.1165/rcmb.2012-0274OC.

162. Yang Y, Cheng Y, Lian Q-Q, Yang L, Qi W, Wu D-R, et al. Contribution of CFTR to alveolar fluid clearance by lipoxin A4 via PI3K/Akt pathway in LPS-induced acute lung injury. Mediators Inflamm. 2013;2013:862628. http://www.hindawi.com/journals/mi/2013/862628/.

163. Wang Q, Zheng X, Cheng Y, Zhang Y-L, Wen H-X, Tao Z, et al. Resolvin D1 stimulates alveolar fluid clearance through alveolar epithelial sodium channel, Na,K-ATPase via ALX/cAMP/PI3K pathway in lipopolysaccharide-induced acute lung injury. J Immunol. 2014;192:3765–77. http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.1302421.

164. Wang Q, Yan S-F, Hao Y, Jin S-W. Specialized pro-resolving mediators regulate alveolar fluid clearance during acute respiratory distress syndrome. Chin Med J (Engl). 2018;131:982. http://www.ncbi.nlm.nih.gov/pubmed/29664060.

165. Morote-Garcia JC, Rosenberger P, Kuhlicke J, Eltzschig HK. HIF-1-dependent repression of adenosine kinase attenuates hypoxia-induced vascular leak. Blood. 2008;111:5571–80. http://www.bloodjournal.org/cgi/doi/10.1182/blood-2007-11-126763.

166. Morote-Garcia JC, Köhler D, Roth JM, Mirakaj V, Eldh T, Eltzschig HK, et al. Repression of the equilibrative nucleoside transporters dampens inflammatory lung injury. Am J Respir Cell Mol Biol. 2013;49:296–305. http://www.atsjournals.org/doi/abs/10.1165/rcmb.2012-0457OC.

167. Köhler D, Streilzenberger A, Morote-García JC, Granja TF, Schneider M, Straub A, et al. Inhibition of adenosine kinase attenuates acute lung injury. Crit Care Med. 2016;44:e181–9. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00032426-900000000-97119.

168. Fuller BM, Mohr NM, Skrupky L, Fowler S, Kollef MH, Carpenter CR. The use of inhaled prostaglandins in patients with ARDS. Chest. 2015;147:1510–22. http://www.ncbi.nlm.nih.gov/pubmed/25742022.

169. Han G, Lu K, Xu W, Zhang S, Huang J, Dai C, et al. Annexin A1-mediated inhibition of inflammatory cytokines may facilitate the resolution of inflammation in acute radiation-induced lung injury. Oncol Lett Spanidios Publications. 2019;18:321–9.

170. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology. 2016;21:14–23. http://www.ncbi.nlm.nih.gov/pubmed/26494423.

171. GOLD Report. Global initiative for chronic obstructive lung diseases (GOLD). 2019. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf.

172. Kim WJ, Lee CY. Environmental exposures and chronic obstructive pulmonary disease. Mol Cell Toxicol. 2017;13:251–5. http://link.springer.com/10.1007/s13273-017-0027-4.

173. Qiao D, Ameli A, Prokopenko D, Chen H, Kho AT, Parker MM, et al. Whole exome sequencing analysis in severe chronic obstructive pulmonary disease. Hum Mol Genet. 2018;27:3801–12. https://academic.oup.com/hmg/article/27/21/3801/5060721.

174. Postma DS, Timens W. Remodeling in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2006;3:434–9. http://www.ncbi.nlm.nih.gov/pubmed/16799088.
175. Bagdonas E, Raudoniute J, Bruzauskaite I, Aldonyte R. Novel aspects of pathogenesis and regeneration mechanisms in COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:995. http://www.ncbi.nlm.nih.gov/pubmed/26082624.

176. Rabe KF, Watz H. Chronic obstructive pulmonary disease. Lancet. 2017;389:1931–40. http://www.ncbi.nlm.nih.gov/pubmed/28513453.

177. Mammen MJ, Sethi S. COPD and the microbiome. Respirology. 2016;21:590–9. http://www.ncbi.nlm.nih.gov/pubmed/26852737.

178. Caramori G, Casolari P, Barczyk A, Durham AL, Di Stefano A, Adcock I. COPD immunopathology. Semin Immunopathol. 2016;38:497–515. http://www.ncbi.nlm.nih.gov/pubmed/27178410.

179. Adcock IM. Role of epigenetic modifications in pathology of COPD. Tanaffos. 2017;16:S2. http://www.ncbi.nlm.nih.gov/pubmed/29158743.

180. Freeman CM, Curtis JL. Lung dendritic cells: shaping immune responses throughout COPD progression. Am J Respir Cell Mol Biol. 2016;56:152–9. http://www.atsjournals.org/doi/10.1165/rcmb.2016-0272TR.

181. Yang X, Huo B, Zhong X, Su W, Liu W, Li Y, et al. Imbalance between subpopulations of regulatory T cells in patients with acute exacerbation of COPD. COPD J Chronic Obstr Pulm Dis. 2017;14:618–25. http://www.ncbi.nlm.nih.gov/pubmed/29166179.

182. Panda SK, Colonna M. Innate lymphoid cells in mucosal immunity. Front Immunol. 2019;10:861. http://www.ncbi.nlm.nih.gov/pubmed/3134050.

183. Poh TY, Mac Aogáin M, Chan AKW, Yiu ACA, Yong VFL, Tiew PY, et al. Understanding COPD-overlap syndromes. Expert Rev Respir Med. 2017;11:285–98. http://www.ncbi.nlm.nih.gov/pubmed/28282995.

184. Faiz A, Heijink IH, Vermeulen CJ, Guryev V, van den Berge M, Navijn MC, et al. Cigarette smoke exposure decreases CFLAR expression in the bronchial epithelium, augmenting susceptibility for lung epithelial cell death and DAMP release. Sci Rep. 2018;8:12426. http://www.ncbi.nlm.nih.gov/pubmed/30127367.

185. Mizumura K, Maruoka S, Shimizu T, Gon Y. Autophagy, selective autophagy, and necroptosis in COPD. Int J Chron Obstruct Pulmon Dis. 2018;13:3165–72. http://www.ncbi.nlm.nih.gov/pubmed/30349225.

186. Küntzi L, Holt GE. Cigarette smoke activates the parthanatos pathway of cell death in human bronchial epithelial cells. Cell Death Dis. 2019;5:127. http://www.nature.com/articles/s41420-019-0205-3.

187. Sauler M, Bazan IS, Lee PJ. Cell death in the lung: the apoptosis—necroptosis axis. Annu Rev Physiol. 2019;81:375–402. http://www.ncbi.nlm.nih.gov/pubmed/30485762.

188. Yoshida M, Minagawa S, Araya J, Sakamoto T, Harai H, Tsubouchi K, et al. Involvement of cigarette smoke-induced epithelial cell ferroptosis in COPD pathogenesis. Nat Commun. 2019;10:3145. http://www.nature.com/articles/s41467-019-10991-7.

189. Pouwels SD, Heijink IH, ten Hacken NH, Vandenabeele P, Krätko DV, Navijn MC, et al. DAMPs activating innate and adaptive immune responses in COPD. Mucosal Immunol. 2014;7:215–26. http://www.ncbi.nlm.nih.gov/pubmed/24150257.

190. Pouwels SD, Hesse L, Faiz A, Lubbers J, Bodha PK, ten Hacken NHT, et al. Susceptibility for cigarette smoke-induced DAMP release and DAMP-induced inflammation in COPD. Am J Physiol Cell Mol Physiol. 2016;311:L881–92. http://www.ncbi.nlm.nih.gov/pubmed/27612964.

191. Brajer-Luftmann B, Nowicka A, Kaczmarek M, Wyrzykiewicz M, Yasar S, Piorunek T, et al. Molecules of damage-associated patterns in bronchoalveolar lavage fluid and serum in chronic obstructive pulmonary disease. Adv Exp Med Biol. 2018;1113:27–35. http://www.ncbi.nlm.nih.gov/pubmed/29429028.

192. Uh S-T, Koo SM, Kim Y, Kim K, Park S, Jang AS, et al. The activation of NLRP3 inflammasome by stimulation of diesel exhaust particles in lung tissues from emphysema model and RAW 264.7 cell line. Korean J Intern Med. 2017;32:865–74. http://www.ncbi.nlm.nih.gov/pubmed/28814068.
193. Zheng R, Tao L, Jian H, Chang Y, Cheng Y, Feng Y, et al. NLRP3 inflammasome activation and lung fibrosis caused by airborne fine particulate matter. Ecotoxicol Environ Saf. 2018;163:612–9. http://www.ncbi.nlm.nih.gov/pubmed/30092543.

194. Wang H, Lv C, Wang S, Ying H, Weng Y, Yu W. NLRP3 Inflammasome involves in the acute exacerbation of patients with chronic obstructive pulmonary disease. Inflammation. 2018;41:1321–33. http://link.springer.com/10.1007/s10753-018-0780-0.

195. Duvall MG, Bruggemann TR, Levy BD. Bronchoprotective mechanisms for specialized pro-resolving mediators in the resolution of lung inflammation. Mol Aspects Med. 2017;58:44–56. http://www.ncbi.nlm.nih.gov/pubmed/28455109.

196. Chen H, Li Z, Dong L, Wu Y, Shen H, Chen Z. Lipid metabolism in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2019;14:1009–18. http://www.ncbi.nlm.nih.gov/pubmed/31190786.

197. Thatcher TH, Woeller CF, McCarthy CE, Sime PJ. Quenching the fires: pro-resolving mediators, air pollution, and smoking. Pharmacol Ther. 2019;197:212–24. http://www.ncbi.nlm.nih.gov/pubmed/30759375.

198. Hsiao H-M, Sapinoro RE, Thatcher TH, Croasdell A, Levy EP, Fulton RA, et al. A novel anti-inflammatory and pro-resolving role for resolvins D1 in acute cigarette smoke-induced lung inflammation. Yildirim AO, editor. PLoS One. 2013;8:e58258. http://dx.plos.org/10.1371/journal.pone.0058258.

199. Fritscher LG, Post M, Rodrigues MT, Silverman F, Balter M, Chapman KR, et al. Profile of eicosanoids in breath condensate in asthma and COPD. J Breath Res. 2012;6:026001. http://stacks.iop.org/1752-7163/6/i=2/a=026001?key=crossref.27de5bd610a6465aab9a684512ec18ce.

200. Croasdell A, Thatcher TH, Kottmann RM, Colas RA, Dalli J, Serhan CN, et al. Resolvins attenuate inflammation and promote resolution in cigarette smoke-exposed human macrophages. Am J Physiol Lung Cell Mol Physiol. 2015;309:L888–901. http://ajplung.physiology.org/lookup/doi/10.1152/ajplung.00125.2015.

201. Ftoh S, Lewington A. Acute Kidney Injury Guideline Development Group convened by the National Clinical Guidelines Centre and commissioned by the National Institute for Health and Care Excellence in association with TRC of PC. Prevention, detection and management of acute kidney injury: concise guideline. Clin Med (Northfield IL). 2014;14:61–5. http://www.ncbi.nlm.nih.gov/pubmed/24532748.

202. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34:1913–7. https://insights.ovid.com/crossref?an=00003246-200607000-00008.

203. Ratanarat R, Skulratanasak P, Tangkwawattanakul N, Hantaweepant C. Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for predicting hospital mortality in critically ill patients with multi-organ dysfunction syndrome. J Med Assoc Thai. 2013;96(Suppl 2):S224–31. http://www.ncbi.nlm.nih.gov/pubmed/23590046.

204. Raup-Konsavage WM, Wang Y, Wang WW, Feliers D, Ruan H, Reeves WB. Neutrophil peptidyl arginine deiminase-4 has a pivotal role in ischemia/reperfusion-induced acute kidney injury. Kidney Int. 2018;93:365–74. http://www.ncbi.nlm.nih.gov/pubmed/29061334.

205. Dellepiane S, Marengo M, Cantaluppi V. Detrimental cross-talk between sepsis and acute kidney injury: new pathogenic mechanisms, early biomarkers and targeted therapies. Crit Care. 2016;20:61. http://ccforum.com/content/20/1/61.

206. Kellum JA, Prowle JR. Paradigms of acute kidney injury in the intensive care setting. Nat Rev Nephrol. 2018;14:217–30. http://www.ncbi.nlm.nih.gov/pubmed/29355173.

207. Raghavan R, Shawar S. Mechanisms of drug-induced interstitial nephritis. Adv Chronic Kidney Dis. 2017;24:64–71. http://www.ncbi.nlm.nih.gov/pubmed/28284381.

208. Markowitz GS, Bomback AS, Perazella MA. Drug-induced glomerular disease: direct cellular injury. Clin J Am Soc Nephrol. 2015;10:1291–9. http://www.ncbi.nlm.nih.gov/pubmed/25862776.

209. Khan S, Loi V, Rosner MH. Drug-induced kidney injury in the elderly. Drugs Aging. 2017;34:729–41. http://link.springer.com/10.1007/s40266-017-0484-4.
210. Wu H, Huang J. Drug-induced nephrotoxicity: pathogenic mechanisms, biomarkers and prevention strategies. Curr Drug Metab. 2018;19:559–67. http://www.ncbi.nlm.nih.gov/pubmed/29119923.

211. Linkermann A, Chen G, Dong G, Kunzendorf U, Krautwald S, Dong Z. Regulated cell death in AKI. J Am Soc Nephrol. 2014;25:2689–701. http://www.jasn.org/cgi/doi/10.1681/ASN.2014030262.

212. Linkermann A, Bräsen JH, Darding M, Jin MK, Sanz AB, Heller J-O, et al. Two independent pathways of regulated necrosis mediate ischemia-reperfusion injury. Proc Natl Acad Sci U S A. 2013;110:12024–9. http://www.pnas.org/cgi/doi/10.1073/pnas.1305538110.

213. von Mässenhausen A, Tonness W, Linkermann A. Cell death pathways drive necroinflammation during acute kidney injury. Nephron. 2018;140(2):144–7. http://www.ncbi.nlm.nih.gov/pubmed/29961062.

214. Anders H-J. Necroptosis in acute kidney injury. Nephron. 2018;139:342–8. http://www.ncbi.nlm.nih.gov/pubmed/29852497.

215. Linkermann A, Stockwell BR, Krautwald S, Anders H-J. Regulated cell death and inflammation: an auto-amplification loop causes organ failure. Nat Rev Immunol. 2014;14:759–67. http://www.nature.com/articles/nri3743.

216. Mulay SR, Linkermann A, Anders H-J. Necroinflammation in kidney disease. J Am Soc Nephrol. 2016;27:27–39. http://www.ncbi.nlm.nih.gov/pubmed/26334031.

217. Letteri JM. Post traumatic acute renal failure. Adv Exp Med Biol. 1987;212:211–8. http://www.ncbi.nlm.nih.gov/pubmed/3303851.

218. Menashe PI, Ross SA, Gottlieb JE. Acquired renal insufficiency in critically ill patients. Crit Care Med. 1988;16:106–9. http://www.ncbi.nlm.nih.gov/pubmed/3168503.

219. Stene JK. Renal failure in the trauma patient. Crit Care Clin. 1990;6:111–9. http://www.ncbi.nlm.nih.gov/pubmed/2404542.

220. de Abreu KLS, Silva Júnior GB, Barreto AGC, Melo FM, Oliveira BB, Mota RMS, et al. Acute kidney injury after trauma: prevalence, clinical characteristics and RIFLE classification. Indian J Crit Care Med. 2010;14:121–8. http://www.ijccm.org/text.asp?2010/14/3/121/74170.

221. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev. 2016;37:85–98. http://www.ncbi.nlm.nih.gov/pubmed/28303073.

222. Sun Y, Johnson C, Zhou J, Wang L, Li YF, Lu Y, et al. Uremic toxins are conditional danger- or homeostasis-associated molecular patterns. Front Biosci (Landmark Ed). 2018;23:348–87. http://www.ncbi.nlm.nih.gov/pubmed/28930551.

223. Mulay SR, Kumar SV, Lech M, Desai J, Anders H-J. How kidney cell death induces renal necroinflammation. Semin Nephrol. 2016;36:162–73. https://linkinghub.elsevier.com/retrieve/pii/S0270929516000243.

224. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. Nat Rev Nephrol. 2011;7:189–200. http://www.ncbi.nlm.nih.gov/pubmed/21364518.

225. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest. 2011;121:4210–21. http://www.jci.org/articles/view/45161.

226. Kanagasundaram NS. Pathophysiology of ischaemic acute kidney injury. Ann Clin Biochem. 2015;52:193–205. http://www.ncbi.nlm.nih.gov/pubmed/25293591.

227. Akcay A, Nguyen Q, Edelstein CL. Mediators of inflammation in acute kidney injury. Mediators Inflamm. 2009;2009:1–12. http://www.ncbi.nlm.nih.gov/pubmed/20182538.

228. Lee DW, Faubel S, Edelstein CL. Cytokines in acute kidney injury (AKI). Clin Nephrol. 2011;76:165–73. http://www.ncbi.nlm.nih.gov/pubmed/21888852.

229. Han HI, Skvarca LB, Espiritu EB, Davidson AJ, Hukriede NA. The role of macrophages during acute kidney injury: destruction and repair. Pediatr Nephrol. 2019;34:561–9. http://link.springer.com/10.1007/s00467-017-3883-1.

230. Wang J, Djudjaj S, Gibbert L, Lennartz V, Breitkopf DM, Rauen T, et al. YB-1 orchestres onset and resolution of renal inflammation via IL10 gene regulation. J Cell Mol Med. 2017;21:3494–505. http://doi.wiley.com/10.1111/jcmm.13260.

231. Bernhardt A, Fehr A, Brandt S, Jercel S, Ballhause TM, Philipson L, et al. Inflammatory cell infiltration and resolution of kidney inflammation is orchestrated by the cold-shock pro-
tein Y-box binding protein-1. Kidney Int. 2017;92:1157–77. https://linkinghub.elsevier.com/retrieve/pii/S0085253817302405.

232. Dessing MC, Pulskens WP, Teske GJ, Butter LM, van der Poll T, Yang H, et al. RAGE does not contribute to renal injury and damage upon ischemia/reperfusion-induced injury. J Innate Immun. 2012;4:80–5. http://www.ncbi.nlm.nih.gov/pubmed/22067944.

233. Li J, Gong Q, Zhong S, Wang L, Guo H, Xiang Y, et al. Neutralization of the extracellular HMGB1 released by ischaemic damaged renal cells protects against renal ischaemia-reperfusion injury. Nephrol Dial Transplant. 2011;26:469–78. https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfq466.

234. Wu H, Steenstra R, de Boer ECS, Zhao CY, Ma J, van der Stelt JM, et al. Preconditioning with recombinant high-mobility group box 1 protein protects the kidney against ischaemia-reperfusion injury in mice. Kidney Int. 2014;85:824–32. http://www.ncbi.nlm.nih.gov/pubmed/24352152.

235. González-Guerrero C, Cannata-Ortiz P, Guerri C, Egido J, Ortiz A, Ramos AM. TLR4-mediated inflammation is a key pathogenic event leading to kidney damage and fibrosis in cyclosporine nephrotoxicity. Arch Toxicol. 2017;91:1925–39. http://www.ncbi.nlm.nih.gov/pubmed/27585667.

236. Park HS, Kim EN, Kim MY, Lim JH, Kim HW, Park CW, et al. The protective effect of neutralizing high-mobility group box 1 against chronic cyclosporine nephrotoxicity in mice. Transpl Immunol. 2016;34:42–9. http://www.ncbi.nlm.nih.gov/pubmed/26603313.

237. Kim J. Poly(ADP-ribose) polymerase activation induces high mobility group box 1 release from proximal tubular cells during cisplatin nephrotoxicity. Physiol Res. 2016;65:333–40. http://www.ncbi.nlm.nih.gov/pubmed/26447520.

238. Tan X, Zheng X, Huang Z, Lin J, Xie C, Lin Y. Involvement of S100A8/A9-TLR4-NLRP3 inflammasome pathway in contrast-induced acute kidney injury. Cell Physiol Biochem. 2017;43:209–22. https://www.karger.com/Article/FullText/480340.

239. Westhoff JH, Seibert FS, Waldherr S, Bauer F, Tönshoff B, Fichtner A, et al. Urinary calprotectin, kidney injury molecule-1, and neutrophil gelatinase-associated lipocalin for the prediction of adverse outcome in pediatric acute kidney injury. Eur J Pediatr. 2017;176:745–55. http://www.ncbi.nlm.nih.gov/pubmed/28409285.

240. Azimi A. Could “calprotectin” and “endocan” serve as “tsroponin of nephrologists”? Med Hypotheses. 2017;99:29–34. http://www.ncbi.nlm.nih.gov/pubmed/28110693.

241. Brooks C, Wei Q, Cho S-G, Dong Z. Regulation of mitochondrial dynamics in acute kidney injury in cell culture and rodent models. J Clin Invest. 2009;119:1275–85. http://www.jci.org/articles/view/37829.

242. Ho PW-L, Pang W-F, Luk CC-W, Ng JK-C, Chow K-M, Kwan BC-H, et al. Urinary mitochondrial DNA level as a biomarker of acute kidney injury severity. Kidney Dis. 2017;3:78–83. http://www.ncbi.nlm.nih.gov/pubmed/28868295.

243. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature. 2010;464:104–7. http://www.nature.com/articles/nature08780.

244. Emma F, Montini G, Parikh SM, Salviali L. Mitochondrial dysfunction in inherited renal disease and acute kidney injury. Nat Rev Nephrol. 2016;12:267–80. http://www.nature.com/articles/nrneph.2015.214.

245. Allam R, Scherbaum CR, Darisipudi MN, Mulay SR, Hägele H, Lichtnekert J, et al. Histones from dying renal cells aggravate kidney injury via TLR2 and TLR4. J Am Soc Nephrol. 2012;23:1375–88. http://www.jasn.org/cgi/doi/10.1681/ASN.20111111077.

246. Nakazawa D, Kumar SV, Marschner J, Desai J, Holderied A, Rath L, et al. Histones and neutrophil extracellular traps enhance tubular necrosis and remote organ injury in ischemic AKI. J Am Soc Nephrol. 2017;28:1753–68. http://www.jasn.org/lookup/doi/10.1681/ASN.2016080925.

247. Silk E, Zhao H, Weng H, Ma D. The role of extracellular histone in organ injury. Cell Death Dis. 2017;8:e2812. http://www.ncbi.nlm.nih.gov/pubmed/28542146.
References

248. Rosin DL, Okusa MD. Dying cells and extracellular histones in AKI: beyond a NET effect? J Am Soc Nephrol. 2012;23:1275–7. http://www.jasn.org/cgi/doi/10.1681/ASN.2012060615.

249. Devuyst O, Olinger E, Rampoldi L. Uromodulin: from physiology to rare and complex kidney disorders. Nat Rev Nephrol. 2017;13:525–44. http://www.ncbi.nlm.nih.gov/pubmed/28781372.

250. Anders H-J, Schaefer L. Beyond tissue injury-damage-associated molecular patterns, Toll-like receptors, and inflammasomes also drive regeneration and fibrosis. J Am Soc Nephrol. 2014;25:1387–400. http://www.ncbi.nlm.nih.gov/pubmed/24762401.

251. Säemann MD, Weichhart T, Zeyda M, Staffler G, Schonn M, Stuhlmieier KM, et al. Tamm–Horsfall glycoprotein links innate immune cell activation with adaptive immunity via a Toll-like receptor-4-dependent mechanism. J Clin Invest. 2005;115:468–75. http://www.ncbi.nlm.nih.gov/pubmed/15650774.

252. Darisipudi MN, Thomasova D, Mulay SR, Brech D, Noessner E, Liapis H, et al. Uromodulin triggers IL-1β-dependent innate immunity via the NLRP3 inflammasome. J Am Soc Nephrol. 2012;23:1783–9. http://www.jasn.org/cgi/doi/10.1681/ASN.2012040338.

253. Wu T-H, Li K-J, Yu C-L, Tsai C-Y. Tamm–Horsfall protein is a potent immunomodulatory molecule and a disease biomarker in the urinary system. Molecules. 2018;23:200. http://www.ncbi.nlm.nih.gov/pubmed/29361765.

254. Mulay SR, Shi C, Ma X, Anders HJ. Novel Insights into crystal-induced kidney injury. Kidney Dis. 2018;4:49–57. http://www.ncbi.nlm.nih.gov/pubmed/29998119.

255. Mulay SR, Kulkarni OP, Rupanagudi KV, Migliorini A, Darisipudi MN, Vilaysane A, et al. Calcium oxalate crystals induce renal inflammation by NLRP3-mediated IL-1β secretion. J Clin Invest. 2013;123:236–46. http://www.jci.org/articles/view/63679.

256. Wu J, Ren J, Liu Q, Hu Q, Wu X, Wang G, et al. Effects of changes in the levels of damage-associated molecular patterns following continuous veno–venous hemofiltration therapy on outcomes in acute kidney injury patients with sepsis. Front Immunol. 2019;9:3052. http://www.ncbi.nlm.nih.gov/pubmed/30666251.

257. Araujo LP, Truzzi RR, Mendes GE, Luz MAM, Burdmann EA, Oliani SM. Interaction of the anti-inflammatory annexin A1 protein and tacrolimus immunosuppressant in the renal function of rats. Am J Nephrol. 2010;31:527–33. http://www.ncbi.nlm.nih.gov/pubmed/2048490.

258. Facio FN, Sena AA, Araújo LP, Mendes GE, Castro I, Luz MAM, et al. Annexin 1 mimetic peptide protects against renal ischemia/reperfusion injury in rats. J Mol Med. 2011;89:51–63. http://www.ncbi.nlm.nih.gov/pubmed/20953576.

259. Araujo LP, Truzzi RR, Mendes GEF, Luz MAM, Burdmann EA, Oliani SM. Annexin A1 protein attenuates cyclosporine-induced renal hemodynamics changes and macrophage infiltration in rats. Inflamm Res. 2012;61:189–96. http://www.ncbi.nlm.nih.gov/pubmed/22101490.

260. Luo R, Kakizoe Y, Wang F, Fan X, Hu S, Yang T, et al. Deficiency of mPGES-1 exacerbates renal fibrosis and inflammation in mice with unilateral ureteral obstruction. Am J Physiol. 2017;312:F121–33. http://www.ncbi.nlm.nih.gov/pubmed/27784694.

261. Bauerle JD, Grenz A, Kim J-H, Lee HT, Eltzschig HK. Adenosine generation and signaling during acute kidney injury. J Am Soc Nephrol. 2011;22:14–20. http://www.ncbi.nlm.nih.gov/pubmed/21209205.

262. Venkatachalal MA, Weinberg JM, Kriz W, Bidani AK. Failed tubule recovery, AKI–CKD transition, and kidney disease progression. J Am Soc Nephrol. 2015;26:1765–76. http://www.ncbi.nlm.nih.gov/pubmed/25810494.

263. Romagnani P, Remuzzi G, Glassock R, Levin A, Jager KJ, Tonelli M, et al. Chronic kidney disease. Nat Rev Dis Primers. 2017;3:17088. http://www.ncbi.nlm.nih.gov/pubmed/29168475.

264. Nogueira A, Pires MJ, Oliveira P. Pathophysiological mechanisms of renal fibrosis: a review of animal models and therapeutic strategies. In Vivo (Brooklyn). 2017;31:1–22. http://www.ncbi.nlm.nih.gov/pubmed/28064215.

265. Higashi AY, Aronow BJ, Dressler GR. Expression profiling of fibroblasts in chronic and acute disease models reveals novel pathways in kidney fibrosis. J Am Soc Nephrol. 2019;30:80–94. http://www.ncbi.nlm.nih.gov/pubmed/30549584.
266. Yuan Q, Tan RJ, Liu Y. Myofibroblast in kidney fibrosis: origin, activation, and regulation. Adv Exp Med Biol. 2019;1165:253–83. http://www.ncbi.nlm.nih.gov/pubmed/31399969.

267. Tang PM-K, Nikolic-Paterson DJ, Lan H-Y. Macrophages: versatile players in renal inflammation and fibrosis. Nat Rev Nephrol. 2019;15:144–58. http://www.nature.com/articles/s41581-019-0110-2.

268. Zhan J, Wang K, Zhang C, Zhang C, Li Y, Zhang Y, et al. GSPE inhibits HMGB1 release, attenuating renal IR-induced acute renal injury and chronic renal fibrosis. Int J Mol Sci. 2016;17:1647. http://www.ncbi.nlm.nih.gov/pubmed/27690015.

269. Lynch J, Nolan S, Slattery C, Feighery R, Ryan MP, McMorrow T. High-mobility group box protein 1: a mediator of inflammatory-induced renal epithelial-mesenchymal transition. Am J Nephrol. 2010;32:590–602. https://www.karger.com/Article/FullText/320485.

270. Zhang M, Guo Y, Fu H, Hu S, Pan J, Wang Y, et al. Chop deficiency prevents UUO-induced renal fibrosis by attenuating fibrotic signals originated from Hmgb1/TLR4/NFκB/IL-1β signaling. Cell Death Dis. 2015;6:e1847. http://www.ncbi.nlm.nih.gov/pubmed/26247732.

271. Tammaro A, Florquin S, Brok M, Claessen N, Butter LM, Teske GJD, et al. S100A8/A9 promotes parenchymal damage and renal fibrosis in obstructive nephropathy. Clin Exp Immunol. 2018;193:361–75. http://www.ncbi.nlm.nih.gov/pubmed/29746703.

272. Li L, Tang W, Yi F. Role of inflammasome in chronic kidney disease. Adv Exp Med Biol. 2019;1165:407–21. http://link.springer.com/10.1007/978-981-13-8871-2_19.

273. Mulay SR, Anders H-J. Crystal nephropathies: mechanisms of crystal-induced kidney injury. Nat Rev Nephrol. 2017;13:226–40. http://www.nature.com/articles/nrneph.2017.10.

274. Komada T, Usui F, Shirasuna K, Kawashima A, Kimura H, Karasawa T, et al. ASC in renal collecting duct epithelial cells contributes to inflammation and injury after unilateral ureteral obstruction. Am J Pathol. 2014;184:1287–98. https://linkinghub.elsevier.com/retrieve/pii/S000294401400087X.

275. Komada T, Chung H, Lau A, Platnich JM, Beck PL, Benediktsson H, et al. Macrophage uptake of necrotic cell DNA activates the AIM2 inflammasome to regulate proinflammatory phenotype in CKD. J Am Soc Nephrol. 2018;29:1165–81. http://www.jasn.org/lookup/doi/10.1681/ASN.2017080863.

276. Neymeyer H, Labes R, Reverte V, Saez F, Stroh T, Dathe C, et al. Activation of annexin A1 signalling in renal fibroblasts exerts antifibrotic effects. Acta Physiol. 2015;215:144–58. http://www.ncbi.nlm.nih.gov/pubmed/26332853.

277. Zhao S, Shen Z, Gao B, Han P. microRNA-206 overexpression inhibits epithelial-mesenchymal transition and glomerulosclerosis in rats with chronic kidney disease by inhibiting JAK/STAT signaling pathway. J Cell Biochem. 2019;120:jcb.28722. http://www.ncbi.nlm.nih.gov/pubmed/31148248.

278. Fontecha-Barriuso M, Martin-Sanchez D, Ruiz-Andres O, Poveda J, Sanchez-Niño MD, Valiño-Rivas L, et al. Targeting epigenetic DNA and histone modifications to treat kidney disease. Nephrol Dial Transplant. 2018;33(11):1875–86. http://www.ncbi.nlm.nih.gov/pubmed/31148248.

279. Chakraborty A, Viswanathan P. Methylation-demethylation dynamics: implications of changes in acute kidney injury. Anal Cell Pathol. 2018;2018:1–16. http://www.ncbi.nlm.nih.gov/pubmed/30073137.

280. Tang J, Zhuang S. Histone acetylation and DNA methylation in ischemia/reperfusion injury. Clin Sci. 2019;133:597–609. http://www.ncbi.nlm.nih.gov/pubmed/30804072.

281. Morgado-Pascual JL, Marchant V, Rodrigues-Diez R, Dolade N, Suarez-Alvarez B, Kerr B, et al. Epigenetic modification mechanisms involved in inflammation and fibrosis in renal pathology. Mediators Inflamm. 2018;2018:1–14. http://www.ncbi.nlm.nih.gov/pubmed/30647531.

282. Bower WA, Johns M, Margolis HS, Williams IT, Bell BP. Population-based surveillance for acute liver failure. Am J Gastroenterol. 2007;102:2459–63. http://www.nature.com/doifinder/10.1111/j.1572-0241.2007.01388.x.

283. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369:2525–34. http://www.ncbi.nlm.nih.gov/pubmed/24369077.
284. Fyfe B, Zaldana F, Liu C. The pathology of acute liver failure. Clin Liver Dis. 2018;22:257–68. https://linkinghub.elsevier.com/retrieve/pii/S1089326118300035.

285. Moreau R. Acute-on-chronic liver failure: a new syndrome in cirrhosis. Clin Mol Hepatol. 2016;22:1–6. http://www.ncbi.nlm.nih.gov/pubmed/27044760.

286. Arroyo V, Moreau R, Kamath PS, Jalan R, Ginès P, Nevens F, et al. Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primers. 2016;2:16041. http://www.nature.com/articles/nrdp201641.

287. Nishikawa H, Osaki Y. Liver cirrhosis: evaluation, nutritional status, and prognosis. Mediators Inflamm. 2015;2015:1–9. http://www.ncbi.nlm.nih.gov/pubmed/26494949.

288. Tittarelli R, Pellegrini M, Scarpellini MG, Marinelli E, Bruti V, di Luca NM, et al. Hepatotoxicity of paracetamol and related fatalities. Eur Rev Med Pharmacol Sci. 2017;21:95–101. http://www.ncbi.nlm.nih.gov/pubmed/28379590.

289. Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 annual report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 32nd annual report. Clin Toxicol (Phila). 2015;53:962–1147. http://www.ncbi.nlm.nih.gov/pubmed/26624241.

290. Lee WM. Recent developments in acute liver failure. Best Pract Res Clin Gastroenterol. 2012;26:3–16. http://www.ncbi.nlm.nih.gov/pubmed/22482521.

291. Akamatsu N, Sugawara Y, Kokudo N. Acute liver failure and liver transplantation. Intractable Rare Dis Res. 2013;2:77–87. http://www.ncbi.nlm.nih.gov/pubmed/2343108.

292. Bernal W, Lee WM, Wendon J, Larsen FS, Williams R. Acute liver failure: a curable disease by 2024? J Hepatol. 2015;62:S112–20. http://linkinghub.elsevier.com/retrieve/pii/S0168827814009374.

293. Koch DG, Speiser JL, Durkalski V, Fontana RJ, Davern T, McGuire B, et al. The natural history of severe acute liver injury. Am J Gastroenterol. 2017;112:1389–96. http://www.ncbi.nlm.nih.gov/pubmed/28440304.

294. Papadopoulos D, Siempis T, Theodorakou E, Tsoulfas G. Hepatic ischemia and reperfusion injury and trauma: current concepts. Arch trauma Res. 2013;2:63–70. http://archtrauma.kaums.ac.ir/article_62138.html.

295. Schwabe RF, Luedde T. Apoptosis and necroptosis in the liver: a matter of life and death. Nat Rev Gastroenterol Hepatol. 2018;15:738–52. http://www.ncbi.nlm.nih.gov/pubmed/30250076.

296. Tsurusaki S, Tsuchiya Y, Koumura T, Nakasone M, Sakamoto T, Matsuoka M, et al. Hepatic ferroptosis plays an important role as the trigger for initiating inflammation in nonalcoholic steatohepatitis. Cell Death Dis. 2019;10:449. http://www.nature.com/articles/s41419-019-1678-y.

297. Li P, He K, Li J, Liu Z, Gong J. The role of Kupffer cells in hepatic diseases. Mol Immunol. 2017;85:222–9. http://www.ncbi.nlm.nih.gov/pubmed/28314211.

298. Li Z, Weinman S. Regulation of hepatic inflammation via macrophage cell death. Semin Liver Dis. 2018;38:340–50. http://www.ncbi.nlm.nih.gov/pubmed/30357771.

299. Guo H, Xie M, Zhou C, Zheng M. The relevance of pyroptosis in the pathogenesis of liver diseases. Life Sci. 2019;223:69–73. http://www.ncbi.nlm.nih.gov/pubmed/30831126.

300. Iorga A, Dara L, Kaplowitz N. Drug-induced liver injury: cascade of events leading to cell death, apoptosis or necrosis. Int J Mol Sci. 2017;18(5):1018. http://www.ncbi.nlm.nih.gov/pubmed/28486401.

301. Iorga A, Dara L. Cell death in drug-induced liver injury. Adv Pharmacol. 2019;85:31–74. http://www.ncbi.nlm.nih.gov/pubmed/31307591.

302. Jaeschke H, Williams CD, Ramachandran A, Bajt ML. Acetaminophen hepatotoxicity and repair: the role of sterile inflammation and innate immunity. Liver Int. 2012;32:8–20. http://doi.wiley.com/10.1111/j.1478-3231.2011.02501.x.

303. Lancaster EM, Hiatt JR, Zarrinpar A. Acetaminophen hepatotoxicity: an updated review. Arch Toxicol. 2015;89:193–9. http://www.ncbi.nlm.nih.gov/pubmed/25537186.

304. Ramachandran A, Jaeschke H. Acetaminophen hepatotoxicity. Semin Liver Dis. 2019;39:221–34. http://www.thieme-connect.de/DOI/DOI?10.1055/s-0039-1679919.
Lee B-W, Jeon B-S, Yoon B-I. Exogenous recombinant human thioredoxin-1 prevents acetaminophen-induced liver injury by scavenging oxidative stressors, restoring the thioredoxin-1 system and inhibiting receptor interacting protein-3 overexpression. J Appl Toxicol. 2018;38:1008–17. http://doi.wiley.com/10.1002/jat.3609.

Paridaens A, Raevens S, Colle I, Bogaerts E, Vandewyncken Y-P, Verhelst X, et al. Combination of tauorsodeoxycholic acid and N-acetylcysteine exceeds standard treatment for acetaminophen intoxication. Liver Int. 2017;37:748–56. http://doi.wiley.com/10.1111/liv.13261.

Jaeschke H, Duan L, Akakpo JY, Farhood A, Ramachandran A. The role of apoptosis in acetaminophen hepatotoxicity. Food Chem Toxicol. 2018;118:709–18. http://www.ncbi.nlm.nih.gov/pubmed/29920288.

Du K, Ramachandran A, Jaeschke H. Oxidative stress during acetaminophen hepatotoxicity: sources, pathophysiological role and therapeutic potential. Redox Biol. 2016;10:148–56. http://www.ncbi.nlm.nih.gov/pubmed/27744120.

Lőrincz T, Jennitz K, Kardon T, Mandl J, Szarka A. Ferroptosis is involved in acetaminophen induced cell death. Pathol Oncol Res. 2015;21:1115–21. http://link.springer.com/10.1007/s12253-015-9946-3.

Abdullah Z, Knolle PA. Liver macrophages in healthy and diseased liver. Pflügers Arch - Eur J Physiol. 2017;469:553–60. http://www.ncbi.nlm.nih.gov/pubmed/28293730.

Lefkowitch JH. The pathology of acute liver failure. Adv Anat Pathol. 2016;23:144–58. http://www.ncbi.nlm.nih.gov/pubmed/27058243.

Li M, Sun X, Zhao J, Xia L, Li J, Xu M, et al. CCL5 deficiency promotes liver repair by improving inflammation resolution and liver regeneration through M2 macrophage polarization. Cell Mol Immunol. 2020;17:753–64. http://www.nature.com/articles/s41423-019-0279-0.

Liu J, Zhang S, Cao H, Wang H, Sun C, Liu S, et al. Deficiency of p38α in macrophage ameliorates d-galactosamine/TNF-α-induced acute liver injury in mice. FEBS J. 2017;284:4200–15. http://doi.wiley.com/10.1111/febs.14294.

Krawitz S, Lingiah V, Pyrsopoulos NT. Acute liver failure. Clin Liver Dis. 2018;22:243–56. http://www.ncbi.nlm.nih.gov/pubmed/29605064.

Rutherford A, Chung RT. Acute liver failure: mechanisms of hepatocyte injury and regeneration. Semin Liver Dis. 2008;28:167–74. http://www.thieme-connect.de/DOI/DOI?10.1055/s-2008-1073116.

Hong J-M, Kim S-J, Lee S-M. Role of necroptosis in autophagy signaling during hepatic ischemia and reperfusion. Toxicol Appl Pharmacol. 2016;308:1–10. http://www.ncbi.nlm.nih.gov/pubmed/27521978.

Sui M, Jiang X, Chen J, Yang H, Zhu Y. Magnesium isoglycyrrhizinate ameliorates liver fibrosis and hepatic stellate cell activation by regulating ferroptosis signaling pathway. Biomed Pharmacother. 2018;106:125–33. http://www.ncbi.nlm.nih.gov/pubmed/29957462.

Al-Khafaji AB, Tohme S, Yazdani HO, Miller D, Huang H, Tsung A. Superoxide induces neutrophil extracellular trap formation in a TLR-4 and NOX-dependent mechanism. Mol Med. 2016;22:1. http://www.ncbi.nlm.nih.gov/pubmed/27453505.

Li Z, Zhao F, Cao Y, Zhang J, Shi P, Sun X, et al. DHA attenuates hepatic ischemia reperfusion injury by inhibiting pyroptosis and activating PI3K/Akt pathway. Eur J Pharmacol. 2018;835:1–10. http://www.ncbi.nlm.nih.gov/pubmed/30075219.

Zhao H, Huang H, Alam A, Chen Q, Suen KC, Cui J, et al. VEGF mitigates histone-induced pyroptosis in the remote liver injury associated with renal allograft ischemia-reperfusion injury in rats. Am J Transplant. 2018;18:1890–903. http://www.ncbi.nlm.nih.gov/pubmed/29446207.

Zhou W-C, Zhang Q-B, Qiao L. Pathogenesis of liver cirrhosis. World J Gastroenterol. 2014;20:7312. http://www.ncbi.nlm.nih.gov/pubmed/24966602.

Koyama Y, Brenner DA. Liver inflammation and fibrosis. J Clin Invest. 2017;127:55–64. http://www.ncbi.nlm.nih.gov/pubmed/28045404.

Yang R, Tonnesseen TI. DAMPs and sterile inflammation in drug hepatotoxicity. Hepatol Int. 2019;13:42–50. http://www.ncbi.nlm.nih.gov/pubmed/30474802.
324. Yang R, Zou X, Tenhunen J, Tønnessen TI. HMGB1 and extracellular histones significantly contribute to systemic inflammation and multiple organ failure in acute liver failure. Mediators Inflamm. 2017;2017:5928078. https://www.hindawi.com/journals/mi/2017/5928078/.

325. Tsung A, Sahai R, Tanaka H, Nakao A, Fink MP, Lotze MT, et al. The nuclear factor HMGB1 mediates hepatic injury after murine liver ischemia-reperfusion. J Exp Med. 2005;201:1135–43. http://www.jem.org/lookup/doi/10.1084/jem.20042614.

326. Huang H, Tohme S, Al-Khafaji AB, Tai S, Loughran P, Chen L, et al. Damage-associated molecular pattern-activated neutrophil extracellular trap exacerbates sterile inflammatory liver injury. Hepatology. 2015;62:600–14. http://doi.wiley.com/10.1002/hep.27841.

327. Basta G, Del Turco S, Navarra T, Lee WM, Acute Liver Failure Study Group. Circulating levels of soluble receptor for advanced glycation end products and ligands of the receptor for advanced glycation end products in patients with acute liver failure. Liver Transplant. 2015;21:847–54. http://www.ncbi.nlm.nih.gov/pubmed/25825217.

328. Yang R, Zou X, Tenhunen J, Tønnessen TI. HMGB1 and extracellular histones significantly contribute to systemic inflammation and multiple organ failure in acute liver failure. Mediators Inflamm. 2017;2017:1–6. http://www.ncbi.nlm.nih.gov/pubmed/28694564.

329. Yang R, Zhang S, Cotoia A, Oksala N, Zhu S, Tenhunen J. High mobility group B1 impairs hepatocyte regeneration in acetaminophen hepatotoxicity. BMC Gastroenterol. 2012;12:45. http://bmcgastroenterol.biomedcentral.com/articles/10.1186/1471-230X-12-45.

330. Lundbäck P, Lea JD, Sowinska A, Ottosson L, Fürst CM, Steen J, et al. A novel high mobility group box 1 neutralizing chimeric antibody attenuates drug-induced liver injury and post-injury inflammation in mice. Hepatology. 2016;64:1699–710. http://doi.wiley.com/10.1002/hep.28736.

331. Martin-Murphy BV, Holt MP, Ju C. The role of damage associated molecular pattern molecules in acetaminophen-induced liver injury in mice. Toxicol Lett. 2010;192:387–94. http://www.ncbi.nlm.nih.gov/pubmed/19931603.

332. Lea JD, Clarke JJ, McGuire N, Antoine DJ. Redox-dependent HMGB1 isoforms as pivotal co-ordinators of drug-induced liver injury: mechanistic biomarkers and therapeutic targets. Antioxid Redox Signal. 2016;24:652–65. http://www.liebertpub.com/doi/10.1089/ars.2015.6406.

333. Dear JW, Clarke JJ, Francis B, Allen L, Wraight J, Shen J, et al. Risk stratification after paracetamol overdose using mechanistic biomarkers: results from two prospective cohort studies lancet. Gastroenterol Hepatol. 2018;35:104–13. https://linkinghub.elsevier.com/retrieve/pii/S2468125317302062.

334. Antoine DJ, Jenkins RE, Dear JW, Williams DP, McGill MR, Sharpe MR, et al. Molecular forms of HMGB1 and keratin-18 as mechanistic biomarkers for mode of cell death and prognosis during clinical acetaminophen hepatotoxicity. J Hepatol. 2012;56:1070–9. https://linkinghub.elsevier.com/retrieve/pii/S0168827812000591.

335. Yamamoto T, Tajima Y. HMGB1 is a promising therapeutic target for acute liver failure. Expert Rev Gastroenterol Hepatol. 2017;11:673–82. http://www.ncbi.nlm.nih.gov/pubmed/28657371.

336. Wen Z, Liu Y, Li F, Ren F, Chen D, Li X, et al. Circulating histones exacerbate inflammation in mice with acute liver failure. J Cell Biochem. 2013;114:2384–91. http://doi.wiley.com/10.1002/jcb.24588.

337. Xu J, Zhang X, Monestier M, Esmon NL, Esmon CT. Extracellular histones are mediators of death through TLR2 and TLR4 in mouse fatal liver injury. J Immunol. 2011;187:2626–31. http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.1003930.

338. Huang H, Chen H-W, Evankovich J, Yan W, Rosborough BR, Nace GW, et al. Histones activate the NLRP3 inflammasome in Kupffer cells during sterile inflammatory liver injury. J Immunol. 2013;191:2665–79. http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.1202733.

339. Wen Z, Lei Z, Yao L, Jiang P, Gu T, Ren F, et al. Circulating histones are major mediators of systemic inflammation and cellular injury in patients with acute liver failure. Cell Death Dis. 2016;7:e2391. http://www.ncbi.nlm.nih.gov/pubmed/27685635.
340. Hayase N, Doi K, Hiruta T, Inokuchi R, Hamaasaki Y, Noiri E, et al. Damage-associated molecular patterns in intensive care unit patients with acute liver injuries. Medicine (Baltimore). 2018;97:e12780. http://www.ncbi.nlm.nih.gov/pubmed/30313098.

341. McGill MR, Sharpe MR, Williams CD, Taha M, Curry SC, Jaeschke H. The mechanism underlying acetaminophen-induced hepatotoxicity in humans and mice involves mitochondrial damage and nuclear DNA fragmentation. J Clin Invest. 2012;122:1574–83. http://www.jci.org/articles/view/59755.

342. Marques PE, Oliveira AG, Pereira RV, David BA, Gomides LF, Saraiva AM, et al. Hepatic DNA deposition drives drug-induced liver injury and inflammation in mice. Hepatology. 2015;61:348–60. http://doi.wiley.com/10.1002/hep.27216.

343. Kono H, Chen C-J, Ontiveros F, Rock KL. Uric acid promotes an acute inflammatory response to sterile cell death in mice. J Clin Invest. 2012;120:1939–49. http://www.jci.org/articles/view/40124.

344. Hoque R, Sohail MA, Salhanick S, Malik AF, Ghani A, Robson SC, et al. P2X7 receptor-mediated purinergic signaling promotes liver injury in acetaminophen hepatotoxicity in mice. Am J Physiol Gastrointest Liver Physiol. 2012;302:G1171–9. http://www.physiology.org/doi/10.1152/ajpgi.00352.2011.

345. Amaral SS, Oliveira AG, Marques PE, Quintão JLD, Pires DA, Resende RR, et al. Altered responsiveness to extracellular ATP enhances acetaminophen hepatotoxicity. Cell Commun Signal. 2013;11:10. http://biosignaling.biomedcentral.com/articles/10.1186/1478-811X-11-10.

346. Locatelli I, Sutti S, Jindal A, Vaccichiao M, Bozzola C, Reutelingsperger C, et al. Endogenous annexin A1 is a novel protective determinant in nonalcoholic steatohepatitis in mice. Hepatology. 2014;60:531–44. http://www.ncbi.nlm.nih.gov/pubmed/24668763.

347. Quiroga J, Prieto J. Liver cytoprotection by prostaglandins. Pharmacol Ther. 1993;58:67–91. http://www.ncbi.nlm.nih.gov/pubmed/815874.

348. O'Brien A, China L, Massey KA, Nicolaou A, Winstanley A, Newson J, et al. Bile duct-ligated mice exhibit multiple phenotypic similarities to acute decompensation patients despite histological differences. Liver Int. 2016;36:837–46. http://www.ncbi.nlm.nih.gov/pubmed/26012885.

349. Erceg D, Kelava T, Cavar I, Pasalić M, Culo F. The effect of cyclic adenosine monophosphate (cAMP) on acute liver toxicity in mice induced by D-galactosamine and lipopolysaccharide. Coll Antropol. 2010;34(Suppl 1):273–7. http://www.ncbi.nlm.nih.gov/pubmed/20402332.

350. Kang J-W, Lee S-M. Resolvin D1 protects the liver from ischemia/reperfusion injury by enhancing M2 macrophage polarization and efferocytosis. Biochim Biophys Acta - Mol Cell Biol Lipids. 1861;2016:1025–35. http://www.ncbi.nlm.nih.gov/pubmed/27317426.

351. Yang X, Zhan Y, Sun Q, Xu X, Kong Y, Zhang J. Adenosine 5′-monophosphate blocks acetaminophen toxicity by increasing ubiquitination-mediated ASK1 degradation. Oncotarget. 2017;8:6273–82. http://www.ncbi.nlm.nih.gov/pubmed/28031524.

352. Wiegand J, Berg T. The etiology, diagnosis and prevention of liver cirrhosis: part 1 of a series on liver cirrhosis. Dtsch Arztebl Int. 2013;110:85–91. https://www.aerzteblatt.de/10.3238/arztebl.2013.0085.
357. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426–37, 1437.e1-9. https://linkinghub.elsevier.com/retrieve/pii/S0016508513002916.

358. Moreau R. The pathogenesis of ACLF: the inflammatory response and immune function. Semin Liver Dis. 2016;36:133–40. http://www.ncbi.nlm.nih.gov/pubmed/27172355.

359. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62:243–52. http://doi.wiley.com/10.1002/hep.27849.

360. Clària J, Arroyo V, Moreau R. The acute-on-chronic liver failure syndrome, or when the innate immune system goes astray. J Immunol. 2016;197:3755–61. http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.1600818.

361. Cai C, Zhu X, Li P, Li J, Gong J, Shen W, et al. NLRP3 deletion inhibits the non-alcoholic steatohepatitis development and inflammation in Kupffer cells induced by palmitic acid. Inflammation. 2017;40:1875–83. http://www.ncbi.nlm.nih.gov/pubmed/28730512.

362. Zhang W-J, Fang Z-M, Liu W-Q. NLRP3 inflammasome activation from Kupffer cells is involved in liver fibrosis of Schistosoma japonicum-infected mice via NF-κB. Parasit Vectors. 2019;12:29. http://www.ncbi.nlm.nih.gov/pubmed/30635040.

363. Ma X, Zheng X, Pan L, Zhang X. NLRP3 inflammasome activation in liver cirrhotic patients. Biochem Biophys Res Commun. 2018;505:40–4. http://www.ncbi.nlm.nih.gov/pubmed/30236988.

364. Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. Nat Rev Gastroenterol Hepatol. 2017;14:397–411. http://www.nature.com/articles/nrgastro.2017.38.

365. Ebrahimi H, Naderian M, Sohrabpour AA. New concepts on reversibility and targeting of liver fibrosis; a review article. Middle East J Dig Dis. 2018;10:133–48. http://www.ncbi.nlm.nih.gov/pubmed/30186577.

366. Parola M, Pinzani M. Liver fibrosis: pathophysiology, pathogenetic targets and clinical issues. Mol Aspects Med. 2019;65:37–55. http://www.ncbi.nlm.nih.gov/pubmed/30213667.

367. Kao Y-H, Jawan B, Goto S, Hung C-T, Lin Y-C, Nakano T, et al. High-mobility group box 1 protein activates hepatic stellate cells in vitro. Transplant Proc. 2008;40:2704–5. http://www.ncbi.nlm.nih.gov/pubmed/18929840.

368. Gaskell H, Ge X, Nieto N. High-mobility group box-1 and liver disease. Hepatol Commun. 2018;2:1005–20. http://www.ncbi.nlm.nih.gov/pubmed/30202816.

369. Ge X, Arriazu E, Magdaleno F, Antoine DJ, dela Cruz R, Theise N, et al. High mobility group box-1 drives fibrosis progression signaling via the receptor for advanced glycation end products in mice. Hepatology. 2018;68:2380–404. http://www.ncbi.nlm.nih.gov/pubmed/29774570.

370. Chen L, Li J, Zhang J, Dai C, Liu X, Wang J, et al. S100A4 promotes liver fibrosis via activation of hepatic stellate cells. J Hepatol. 2015;62:156–64. http://www.ncbi.nlm.nih.gov/pubmed/25111176.

371. Jiang S, Zhang Y, Zheng J-H, Li X, Yao Y-L, Wu Y-L, et al. Potentiation of hepatic stellate cell activation by extracellular ATP is dependent on P2X7R-mediated NLRP3 inflammasome activation. Pharmacol Res. 2017;117:82–93. http://www.ncbi.nlm.nih.gov/pubmed/27940204.

372. Yaping Z, Ying W, Luqin D, Ning T, Xuemai A, Xixian Y. Mechanism of interleukin-1β-induced proliferation in rat hepatic stellate cells from different levels of signal transduction. APMIS. 2014;122:392–8. http://www.ncbi.nlm.nih.gov/pubmed/23992404.

373. Xu F, Liu C, Zhou D, Zhang L. TGF-β/SMAD pathway and its regulation in hepatic fibrosis. J Histochem Cytochem. 2016;64:157–67. http://www.ncbi.nlm.nih.gov/pubmed/26747705.

374. Musso G, Gambino R, Cassader M, Paschetta E, Sircana A. Specialized proresolving mediators: enhancing nonalcoholic steatohepatitis and fibrosis resolution. Trends Pharmacol Sci. 2018;39:387–401. https://linkinghub.elsevier.com/retrieve/pii/S0165614718300269.

375. Jung YK, Yim HJ. Reversal of liver cirrhosis: current evidence and expectations. Korean J Intern Med. 2017;32:213–28. http://kjim.org/journal/view.php?doi=10.3904/kjim.2016.268.
376. Poznyak V, Rekve DE. WHO | Global status report on alcohol and health 2018. WHO World Health Organization. 2018. https://www.who.int/substance_abuse/publications/global_alcohol_report/en/.

377. Lieber C. Alcoholic liver disease: new insights in pathogenesis lead to new treatments. J Hepatol. 2000;32:113–28. http://www.ncbi.nlm.nih.gov/pubmed/10728799.

378. Osna NA, Donohue TM, Kharbanda KK. Alcoholic liver disease: pathogenesis and current management. Alcohol Res. 2017;38:147–61. http://www.ncbi.nlm.nih.gov/pubmed/28988570.

379. Miniño AM, Heron MP, Smith BL. Deaths: preliminary data for 2004. Natl Vital Stat Rep. 2006;54:1–49. http://www.ncbi.nlm.nih.gov/pubmed/16850709.

380. Stickel F, Datz C, Hampe J, Bataller R. Pathophysiology and management of alcoholic liver disease: update 2016. Gut Liver. 2017;11:173–88. http://www.ncbi.nlm.nih.gov/pubmed/28274107.

381. Parlesak A, Schäfer C, Schütz T, Bode JC, Bode C. Increased intestinal permeability to macromolecules and endotoxemia in patients with chronic alcohol abuse in different stages of alcohol-induced liver disease. J Hepatol. 2000;32:742–7. http://www.ncbi.nlm.nih.gov/pubmed/10845660.

382. Rao R. Endotoxemia and gut barrier dysfunction in alcoholic liver disease. Hepatology. 2009;50:638–44. http://doi.wiley.com/10.1002/hep.23009.

383. Hartmann P, Seebauer CT, Schnabl B. Alcoholic liver disease: the gut microbiome and liver cross talk. Alcohol Clin Exp Res. 2015;39:763–75. http://doi.wiley.com/10.1111/acer.12704.

384. Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, et al. The gut–liver axis and the intersection with the microbiome. Nat Rev Gastroenterol Hepatol. 2018;15:397–411. http://www.ncbi.nlm.nih.gov/pubmed/29748586.

385. Wang S, Pacher P, De Lisle RC, Huang H, Ding W-X. A mechanistic review of cell death in alcohol-induced liver injury. Alcohol Clin Exp Res. 2016;40:1215–23. http://www.ncbi.nlm.nih.gov/pubmed/27130888.

386. Gao B, Ahmad MF, Nagy LE, Tsukamoto H. Inflammatory pathways in alcoholic steatohepatitis. J Hepatol. 2019;70:249–59. http://www.ncbi.nlm.nih.gov/pubmed/30658726.

387. Mihm S. Danger-associated molecular patterns (DAMPs): molecular triggers for sterile inflammation in the liver. Int J Mol Sci. 2018;19:3104. http://www.mdpi.com/1422-0067/19/10/3104.

388. Zhou Z, Ye TJ, Bonavita G, Daniels M, Kainrad N, Jorgasuria A, et al. Adipose-specific lipin-1 overexpression renders hepatic ferroptosis and exacerbates alcoholic steatohepatitis in mice. Hepatol Commun. 2019;3:656–69. http://www.ncbi.nlm.nih.gov/pubmed/31061954.

389. Ge X, Antoine DJ, Lu Y, Arriazu E, Leung T-M, Klepper AL, et al. High mobility group box-1 (HMGB1) participates in the pathogenesis of alcoholic liver disease (ALD). J Biol Chem. 2014;289:22672–91. http://www.ncbi.nlm.nih.gov/pubmed/24928512.

390. Saha B, Tornai D, Kodys K, Adejumo A, Lowe P, McClain C, et al. Biomarkers of macrophage activation and immune danger signals predict clinical outcomes in alcoholic hepatitis. Hepatology. 2019;70(4):1134–49. http://www.ncbi.nlm.nih.gov/pubmed/30891779.

391. Sacleux S-C, Samuel D. A critical review of MELD as a reliable tool for transplant prioritization. Semin Liver Dis. 2019;39(4):403–13. http://www.ncbi.nlm.nih.gov/pubmed/31242526.

392. Szabo G, Csak T. Inflammasomes in liver diseases. J Hepatol. 2012;57:642–54. https://linkinghub.elsevier.com/retrieve/pii/S0168827812003340.

393. Petrasek J, Iracheta-Vellve A, Saha B, Sathishchandran A, Kodys K, Fitzgerald KA, et al. Metabolic danger signals, uric acid and ATP, mediate inflammatory cross-talk between hepatocytes and immune cells in alcoholic liver disease. J Leukoc Biol. 2015;98:249–56. http://doi.wiley.com/10.1189/jlb.3AB1214-590R.

394. Heo MJ, Kim TH, You JS, Blaya D, Sancho-Bru P, Kim SG. Alcohol dysregulates miR-148a in hepatocytes through FoxO1, facilitating pyroptosis via TXNIP overexpression. Gut. 2019;68:708–20. http://www.ncbi.nlm.nih.gov/pubmed/29475852.

395. Bataller R, Gao B. Liver fibrosis in alcoholic liver disease. Semin Liver Dis. 2015;35:146–56. http://www.ncbi.nlm.nih.gov/pubmed/25974900.
References

396. Karvellas CJ, Tillman H, Leung AA, Lee WM, Schilsky ML, Hameed B, et al. Acute liver injury and acute liver failure from mushroom poisoning in North America. Liver Int. 2016;36:1043–50. http://www.ncbi.nlm.nih.gov/pubmed/26837055.

397. Debi U, Kaur R, Prasad KK, Sinha SK, Sinha A, Singh K. Pancreatic trauma: a concise review. World J Gastroenterol. 2013;19:9003. http://www.ncbi.nlm.nih.gov/pubmed/24379625.

398. Klochkov A, Sun Y. Alcoholic Pancreatitis. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2020. http://www.ncbi.nlm.nih.gov/pubmed/30725876.

399. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet (London, England). 2015;386:85–96. https://linkinghub.elsevier.com/retrieve/pii/S0140673614606498.

400. Clemens DL, Schneider KJ, Arkfeld CK, Grode KR, Wells MA, Singh S. Alcoholic pancreatitis: new insights into the pathogenesis. World J Gastrointest Pathophysiol. 2016;7:48–58. http://www.wjgnet.com/2150-5330/full/v7/i1/48.htm.

401. Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016;387:1957–66. http://www.ncbi.nlm.nih.gov/pubmed/26948434.

402. Pham A, Forsmark C. Chronic pancreatitis: review and update of etiology, risk factors, and management. F1000Research. 2018;7:607. http://www.ncbi.nlm.nih.gov/pubmed/29946424.

403. Fortunato F, Kromer G. Impaired autophagosome-lysosome fusion in the pathogenesis of pancreatitis. Autophagy. 2009;5:850–3. http://www.ncbi.nlm.nih.gov/pubmed/19458481.

404. Gu H, Werner J, Bergmann F, Whitcomb DC, Büchler MW, Fortunato F. Necro-inflammatory response of pancreatic acinar cells in the pathogenesis of acute alcoholic pancreatitis. Cell Death Dis. 2013;4:e816. http://www.ncbi.nlm.nih.gov/pubmed/24091659.

405. Ren Z, Wang X, Xu M, Yang F, Frank JA, Ke Z, et al. Binge ethanol exposure causes endoplasmic reticulum stress, oxidative stress and tissue injury in the pancreas. Oncotarget. 2016;7:54303–16. http://www.ncbi.nlm.nih.gov/pubmed/27527870.

406. Kang R, Lotze MT, Zeh HJ, Billiar TR, Tang D. Cell death and DAMPs in acute pancreatitis. Mol Med. 2014;20:466–77. http://www.ncbi.nlm.nih.gov/pubmed/25105302.

407. Merrick MA. Secondary injury after musculoskeletal trauma: a review and update. J Athl Train. 2002;37:209–17. http://www.ncbi.nlm.nih.gov/pubmed/16558673.

408. Kobbe P, Vodovotz Y, Kaczorowski DJ, Billiar TR, Pape H-C. The role of fracture-associated soft tissue injury in the induction of systemic inflammation and remote organ dysfunction after bilateral femur fracture. J Orthop Trauma. 2008;22:385–90. https://insights.ovid.com/crossref?an=00005131-200807000-00003.

409. Einhorn TA, Gerstenfeld LC. Fracture healing: mechanisms and interventions. Nat Rev Rheumatol. 2015;11:45–54. http://www.ncbi.nlm.nih.gov/pubmed/25266456.

410. Hauser CJ, Zhou X, Joshi P, Cuchens MA, Kregor P, Devidas M, et al. The immune microenvironment of human fracture/soft-tissue hematomas and its relationship to systemic immunity. J Trauma. 1997;42:895–903; discussion 903-4. http://www.ncbi.nlm.nih.gov/pubmed/9191672.

411. Bastian O, Pillay J, Alblass J, Leenen L, Koenderman L, Blokhuis T. Systemic inflammation and fracture healing. J Leukoc Biol. 2011;89:669–73. http://www.ncbi.nlm.nih.gov/pubmed/21208896.

412. Kobbe P, Vodovotz Y, Kaczorowski DJ, Mollen KP, Billiar TR, Pape H-C. Patterns of cytokine release and evolution of remote organ dysfunction after bilateral femur fracture. Shock. 2008;30:43–7. https://insights.ovid.com/crossref?an=00024382-200807000-00008.

413. Levy RM, Prince JM, Yang R, Mollen KP, Liao H, Watson GA, et al. Systemic inflammation and remote organ damage following bilateral femur fracture requires Toll-like receptor 4. Am J Physiol Regul Integr Comp Physiol. 2006;291:R970–6. http://www.physiology.org/doi/10.1152/ajpregu.00793.2005.

414. Pfeifer R, Darwiche S, Kohut L, Billiar TR, Pape H-C. Cumulative effects of bone and soft tissue injury on systemic inflammation: a pilot study. Clin Orthop Relat Res. 2013;471:2815–21. http://www.ncbi.nlm.nih.gov/pubmed/23479238.

415. Levy RM, Mollen KP, Prince JM, Kaczorowski DJ, Vallabhanei R, Liu S, et al. Systemic inflammation and remote organ injury following trauma require HMGB1. Am J Physiol
416. Sirait R, Hatta M, Ramli M, Islam A, Arief S. Systemic lidocaine inhibits high-mobility group box 1 messenger ribonucleic acid expression and protein in BALB/c mice after closed fracture musculoskeletal injury. Saudi J Anaesth. 2018;12:395. http://www.ncbi.nlm.nih.gov/pubmed/30100837.

417. Degos V, Maze M, Vacas S, Hirsch J, Guo Y, Shen F, et al. Bone fracture exacerbates murine ischemic cerebral injury. Anesthesiology. 2013;118:1362–72. http://anesthesiology.pubs.asahq.org/Article.aspx?doi=10.1097/ALN.0b013e31828c23f8.

418. Tsai W-H, Huang S-T, Liu W-C, Chen L-W, Yang K-C, Hsu K-C, et al. High risk of rhabdomyolysis and acute kidney injury after traumatic limb compartment syndrome. Ann Plast Surg. 2015;74:S158–61. http://www.ncbi.nlm.nih.gov/pubmed/25785380.

419. Torres PA, Helmstetter JA, Kaye AM, Kaye AD. Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner J. 2015;15:58–69. http://www.ncbi.nlm.nih.gov/pubmed/25829882.

420. Huang R-S, Zhou J-J, Feng Y-Y, Shi M, Guo F, Hou S-J, et al. Pharmacological inhibition of macrophage Toll-like receptor 4/nuclear factor-kappa B alleviates rhabdomyolysis-induced acute kidney injury. Chin Med J (Engl). 2017;130:2163. http://www.ncbi.nlm.nih.gov/pubmed/28836571.

421. Chen L, Zhao H, Alam A, Mi E, Eguchi S, Yao S, et al. Postoperative remote lung injury and its impact on surgical outcome. BMC Anesthesiol. 2019;19:30. http://www.ncbi.nlm.nih.gov/pubmed/30832647.

422. Sanchez-Adams J, Leddy HA, McNulty AL, O’Connor CJ, Guilak F. The mechanobiology of articular cartilage: bearing the burden of osteoarthritis. Curr Rheumatol Rep. 2014;16(10):451.

423. Anderson DE, Johnstone B. Dynamic mechanical compression of chondrocytes for tissue engineering: a critical review. Front Bioeng Biotechnol. 2017;5:76. http://www.ncbi.nlm.nih.gov/pubmed/29322043.

424. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthr Cartil. 2010;18:24–33. https://doi.org/10.1016/j.joca.2009.08.010.

425. Robinson WH, Leps CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12:580–92. http://www.ncbi.nlm.nih.gov/pubmed/27539668.

426. Jonsson H, Olausdottir S, Sigurdardottir S, Aspelund T, Eiriksdottir G, Sigurdsson S, et al. Incidence and prevalence of total joint replacements due to osteoarthritis in the elderly: risk factors and factors associated with late life prevalence in the AGES-Reykjavik Study. BMC Musculoskelet Disord. 2016;17:14. http://www.ncbi.nlm.nih.gov/pubmed/26759053.

427. Hwang HS, Kim HA. Chondrocyte apoptosis in the pathogenesis of osteoarthritis. Int J Mol Sci. 2015;16(11):26035–54. https://doi.org/10.3390/ijms161125943.

428. Riegger J, Brenner RE. Evidence of necroptosis in osteoarthritic disease: investigation of blunt mechanical impact as possible trigger in regulated necrosis. Cell Death Dis. 2019;10:683. https://doi.org/10.1038/s41419-019-1930-5.

429. Zhao L-R, Xing R-L, Wang P-M, Zhang N-S, Yin S-J, Li X-C, et al. NLRLP1 and NLRLP3 inflammasomes mediate LPS/ATP-induced pyroptosis in knee osteoarthritis. Mol Med Rep. 2018;17:5463–9. http://www.ncbi.nlm.nih.gov/pubmed/29393464.

430. Lepetsos P, Papavissiliou AG. ROS/oxidative stress signaling in osteoarthritis. Biochim Biophys Acta. 2016;1862:576–91. https://doi.org/10.1016/j.bbadis.2016.01.003.

431. Abusarah J, Bentz M, Benabdoune H, Rondon PE, Shi Q, Fernandes JC, et al. An overview of the role of lipid peroxidation-derived 4-hydroxynonenal in osteoarthritis. Inflamm Res. 2017;66(8):637–51.
Hügle T, Geurts J. What drives osteoarthritis—synovial versus subchondral bone pathology. Rheumatology (Oxford). 2017;56:1461–71. [PubMed:28003493].

Griffin TM, Scanzello CR. Innate inflammation and synovial macrophages in osteoarthritis pathophysiology. Clin Exp Rheumatol. 2019;37(Suppl 1):57–63. [PubMed:31621560].

Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis. 2013;5:77–94. [PubMed:23641259].

Rosenberg JH, Rai V, Dilisio MF, Agrawal DK. Damage-associated molecular patterns in the pathogenesis of osteoarthritis: potentially novel therapeutic targets. Mol Cell Biochem. 2017;434:171–9. [PubMed:29338452].

Mahon OR, Kelly DJ, McCarthy GM, Dunne A. Osteoarthritis-associated basic calcium phosphate crystals alter immune cell metabolism and promote M1 macrophage polarization. Osteoarthr Cartil. 2019;28(5):603–12. [PubMed:31730805].

Dadas A, Washington J, Díaz-Arrastia R, Janigro D. Biomarkers in traumatic brain injury (TBI): a review. Neuropsychiatr Dis Treat. 2018;14:2989–3000. [PubMed:30510421].

Wang KK, Yang Z, Zhu T, Shi Y, Rubenstein R, Tyndall JA, et al. An update on diagnostic and prognostic biomarkers for traumatic brain injury. Expert Rev Mol Diagn. 2018;18:165–80. [PubMed:29338452].

Posti JP, Takala RSK, Lagerstedt L, Dickens AM, Mohammadian M, et al. Correlation of blood biomarkers and biomarker panels with traumatic findings on computed tomography after traumatic brain injury. J Neurotrauma. 2019;36:2178–89. [PubMed:28060212].

Paudel YN, Shaikh MF, Chakraborti A, Kumari Y, Aledo-Serrano Á, Aleksovska K, et al. HMGB1: a common biomarker and potential target for TBI, neuroinflammation, epilepsy, and cognitive dysfunction. Front Neurosci. 2018;12:628. [PubMed:29338452].

Hu Q, Ren J, Wu J, Li G, Wu X, Liu S, et al. Urinary mitochondrial DNA levels identify acute kidney injury in surgical critical illness patients. Shock. 2017;48:11–7. [PubMed:29338452].

Whitaker RM, Stallons LJ, Kneff JE, Alge JL, Harmon JL, Rahn JJ, et al. Urinary mitochondrial DNA is a biomarker of mitochondrial disruption and renal dysfunction in acute kidney injury. Kidney Int. 2015;88:1336–44. [PubMed:26287315].

Clarke JJ, Dear JW, Antoine DJ. Recent advances in biomarkers and therapeutic interventions for hepatic drug safety – false dawn or new horizon? Expert Opin Drug Saf. 2016;15:1–10. [PubMed:26923482].

Yang L, Wang F, Yang L, Yuan Y, Chen Y, Zhang G, et al. HMGB1 a-box reverses brain edema and deterioration of neurological function in a traumatic brain injury mouse model. Cell Physiol Biochem. 2018;46:2532–42. [PubMed:28060212].

Kobayashi M, Tamari K, Al Salihi MO, Nishida K, Takeuchi K. Anti-high mobility group box 1 antibody suppresses local inflammatory reaction and facilitates olfactory nerve recovery following injury. J Neuroinflammation. 2018;15:124. [PubMed:28060212].

Okuma Y, Wake H, Teshigawara K, Takahashi Y, Hishikawa T, Yasuhara T, et al. Anti-high mobility group box 1 antibody therapy may prevent cognitive dysfunction after traumatic brain injury. World Neurosurg. 2019;122:e864–71. [PubMed:28060212].

Gao T, Chen Z, Chen H, Yuan H, Wang Y, Peng X, et al. Inhibition of HMGB1 mediates neuroprotection of traumatic brain injury by modulating the microglia/macrophage polarization. Biochem Biophys Res Commun. 2018;497:430–6. [PubMed:28060212].
Yan B, Chen F, Xu L, Xing J, Wang X. HMGB1-TLR4-IL23-IL17A axis promotes paraquat-induced acute lung injury by mediating neutrophil infiltration in mice. Sci Rep. 2017;7:597. http://www.ncbi.nlm.nih.gov/pubmed/28377603.

Shimazaki J, Matsumoto N, Ogura H, Muoya T, Kuwagata Y, Nakagawa J, et al. Systemic involvement of high-mobility group box 1 protein and therapeutic effect of anti-high-mobility group box 1 protein antibody in a rat model of crush injury. Shock. 2012;37:634–8. http://www.ncbi.nlm.nih.gov/pubmed/22392147.

Lau A, Wang S, Liu W, Haig A, Zhang Z-X, Jevnikar AM. Glycyrrhizic acid ameliorates HMGB1-mediated cell death and inflammation after renal ischemia reperfusion injury. Am J Nephrol. 2014;40:84–95. http://www.ncbi.nlm.nih.gov/pubmed/25059568.

Zhu F, Chong Lee Shin OL, Xu H, Zhao Z, Pei G, Hu Z, et al. Melatonin promoted renal regeneration in folic acid-induced acute kidney injury via inhibiting nucleocytoplasmic translocation of HMGB1 in tubular epithelial cells. Am J Transl Res. 2017;9:1694–707. http://www.ncbi.nlm.nih.gov/pubmed/28469775.

Bisicchia E, Sasso V, Catanzaro G, Leuti A, Besharat ZM, Chiacchiarini M, et al. Resolvin D1 halts remote neuroinflammation and improves functional recovery after focal brain damage via ALX/FPR2 receptor-regulated microRNAs. Mol Neurobiol. 2018;55:6894–905. http://www.ncbi.nlm.nih.gov/pubmed/29357041.

Liao W-I, Wu S-Y, Wu G-C, Pao H-P, Tang S-E, Huang K-L, et al. Ac2-26, an annexin A1 peptide, attenuates ischemia-reperfusion-induced acute lung injury. Int J Mol Sci. 2017;18:1771. http://www.ncbi.nlm.nih.gov/pubmed/28809781.

Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. J Clin Invest. 2018;128:2657–69. http://www.ncbi.nlm.nih.gov/pubmed/29757195.