Danger Control Programs Cause Tissue Injury and Remodeling

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Abstract: Are there common pathways underlying the broad spectrum of tissue pathologies that develop upon injuries and from subsequent tissue remodeling? Here, we explain the pathophysiological impact of a set of evolutionary conserved danger control programs for tissue pathology. These programs date back to the survival benefits of the first multicellular organisms upon traumatic injuries by launching a series of danger control responses, i.e., 1. Haemostasis, or clotting to control bleeding; 2. Host defense, to control pathogen entry and spreading; 3. Re-epithelialisation, to recover barrier functions; and 4. Mesenchymal, to repair to regain tissue stability. Taking kidney pathology as an example, we discuss how clotting, inflammation, epithelial healing, and fibrosis/sclerosis determine the spectrum of kidney pathology, especially when they are insufficiently activated or present in an overshooting and deregulated manner. Understanding the evolutionary benefits of these response programs may refine the search for novel therapeutic targets to limit organ dysfunction in acute injuries and in progressive chronic tissue remodeling.

Keywords: regeneration; fibrosis; coagulation; stem cells; inflammation; acute kidney injury; chronic kidney disease; healing; repair
1. Introduction

Most acute and chronic disorders involve a combination of direct and indirect tissue injuries, i.e., the damage caused by the injurious trigger, and that caused by a series of different danger response programs, i.e., clotting, inflammation, epithelial regeneration, and mesenchymal repair. These processes predominate in a serial manner during acute disorders, with some overlap. However, in chronic non-communicable diseases this overlap turns into a concomitant persistence of some of these programs, e.g., inflammation and healing, which often leads to significant parenchymal atrophy and fibrosis. In this review we use kidney pathology as an example for the spectrum of pathological manifestations that derive from these danger response programs and explain why evolution’s risk-benefit assessment conserved them across species over time. Better understanding of the origin of tissue pathologies should be instrumental to better define target pathways for therapeutic interventions.

2. Injuries Trigger a Series of Host Response Programs

Wounding requires immediate actions to control the dangers that come with the injury followed either by regeneration or repair, a concept that applies to plants and animals [1,2]. Focal wounding requires local danger control, e.g., of pathogen entry, to prevent systemic consequences such as fatal sepsis. Hence, such survival benefits from local danger control, outweighs any risk of focal collateral injury or tissue remodeling that comes with these danger responses. What remains problematic are systemic triggers of danger responses, such as toxic (drugs), hemodynamic (shock or arterial hypertension), or metabolic alterations (diabetes, hyperlipidemia) because these induce responses that affect multiple organ systems and organ compartments, which implies that any collateral damage threatens entire organs, if not the whole body. In the following paragraphs we will introduce the four major danger response programs along wound healing after acute skin injury [3–5].

2.1. Clotting Addresses the Risk of Potentially Fatal Bleeding

Skin injury causes bleeding, which implies the risk of dying from hemorrhagic shock. Clotting addresses this type of danger within minutes by haemolymph aggregation in arthropods, and by a more sophisticated interplay of injured endothelial cells, coagulation factors, and platelets in vertebrates [6–9]. Overshooting clotting causes tissue ischemia via intravascular coagulation or thromboembolism.

2.2. Inflammation Addresses the Risk of Fatal Sepsis

The balance between microbe virulence and host defense has gained considerable complexity along the evolution of monocellular organisms [10–13]. Outer surface wounding allows pathogen entry and may lead to fatal sepsis, if not immediately addressed by local inflammation to control pathogen spreading [14,15]. Extrinsic pathogen-associated molecular patterns (PAMPs) and intrinsic damage-associated molecular patterns (DAMPs) act as alarmins that activate the same innate immunity pattern recognition receptors in infectious or sterile inflammations [16–21]. Inflammation is already activated by clotting, a process referred to as immunothrombosis [6,22–24], as platelet aggregates release chemokines that trigger the recruitment of neutrophils [6,25,26]. Overshooting local inflammation causes unnecessary immunopathology and loss of parenchyma, e.g., in pyoderma...
gangraenosum [27,28]. Overshooting systemic inflammation contributes to the early phase of sepsis, while insufficient systemic inflammation accounts for lethality in the late phase of sepsis [14,29].

2.3. Epithelial Regeneration Restores Barrier Functions

Non-sterile barrier defects require rapid regeneration of the barrier to limit pathogen entry [5,30]. Epithelial barriers have also other important functions, such as nutrient absorption (gut), gas transfer (lungs), or solute secretion/re-absorption (kidney), which require rapid restoration upon injury, e.g., by signals that trigger re-epithelialisation from wound borders [2,5,31]. Components of the coagulation cascade are the first mediators inside a wound that elicit mitogenic effects on the surviving epithelial cells [2,7,25,31,32]. Inflammatory mediators with mitogenic properties, such as epithelial growth factors, hepatocyte growth factor, IL-6, IL-17, fractalkine, CXCL10, and IL-22, as well as certain miRNAs, stimulate epithelial repair [31,33–40]. Local progenitor cells that are committed to the specific epithelial lineage phenotype contribute to re-epithelialisation [30,40–42]. Insufficient re-epithelialisation creates chronic wounds, which implies a risk of infections, while overshooting or uncoordinated re-epithelialisation, can also cause, problematically, hyperplastic lesions [2,43].

2.4. Mesenchymal Repair Restores Tissue Stability

Insufficient re-epithelialisation, loss of tissue parenchyma, or injury to mesenchymal tissues activates the wound healing program of mesenchymal repair. This process is needed to stabilize the organ’s shape and structure. Insufficient epithelial repair directly stimulates mesenchymal healing, as epithelial-mesenchymal transition (EMT) of epithelial cells, and their arrest in the G2/M phase of the cell cycle induce the secretion of the pro-fibrotic cytokine TGF-β [44]. The associated accumulation of collagen-producing cells [45,46] relates to an influx of bone marrow-derived fibrocytes [47,48], a mesenchymal transition of also pericytes and endothelial cells [48,49], as well as the proliferation of resident fibroblasts that transform to myofibroblasts [49]. The accumulation of extracellular matrix (referred to as fibrosis) stiffens the tissue (referred to as sclerosis). Insufficient mesenchymal healing destabilizes tissues while overshooting mesenchymal healing produces fibrotic lesions such as keloid, and diffuse fibrotic disorders such as scleroderma.

In the following we discuss how these ancient danger control programs account for the spectrum of organ abnormalities known from pathology textbooks. Based on our own experience we focus to kidney pathology. We describe in more detail how common histomorphological abnormalities and disease entities develop, either from insufficient, or overshooting danger control programs (Figure 1).
Figure 1. Insufficient and predominant danger response programs determine kidney pathology. Distinct entities of clinical syndromes or kidney injury patterns are consequences of insufficient or overshooting danger control programs.

### 3. Clotting

#### 3.1. Overshooting Clotting in the Kidney

Thrombotic microangiopathies that affect the kidney result from an abnormal activation of microvessel endothelial cells, and subsequent activation of platelets and plasmatic coagulation (Figure 2) [50,51]. Microvascular clotting causes tissue ischemia and necrosis. In crescentic glomerulonephritis, vascular necrosis leads to perforations, ruptures in the glomerular basement membrane (GBM), plasma leakage, and bleeding [52]. Glomerular bleeding manifests clinically as hematuria, a process that should activate clotting inside the glomerulus. In fact, fibrin deposition is usually seen in areas of loop necrosis in crescentic glomerulonephritis, in turn, used as a diagnostic marker to identify necrotizing glomerulonephritis [53,54]. In Alport nephropathy, a genetic GBM abnormality not associated with intense inflammation, progressive intrinsic degradation and disintegration of the GBM, generates similar GBM perforations and ruptures that are associated with hematuria, fibrin deposits, and plasma leakage [43]. As part of the clot formation, activated platelets release pro-inflammatory and mitogenic factors, which activate subsequent inflammation as well as epithelial regeneration [7,25,26,31,55]. The link of clotting and inflammation, referred to as immunothrombosis, is well defined in the field of immunology and currently understood as a mechanism to limit pathogen spreading from the entry site [6,56–59]. This evolutionary conserved process certainly contributes to atherosclerosis and -thrombosis, and it is reasonable to assume that this link is as important in other non-communicable disorders.

#### 3.2. Insufficient Clotting in the Kidney

IgA nephropathy, and several other renal disorders, may present with intermittent macrohematuric episodes, implicating that vascular sealing by clotting is insufficient [60]. Urokinase expression further down the urinary tract elicits fibrinolytic activity that may maintain the bleeding [61].
Figure 2. Overshooting clotting in thrombotic microangiopathy. Local activation microvascular endothelial cells and lack of distinct inhibitory factors can lead to thrombotic microangiopathy which is characterized by microthrombi obstructing arteriolar and glomerular vessels, a lesion associated with significant inflammatory cell infiltrates (left). Fibrin immunostaining displayes clot formation within glomeruli (right). Original magnification 200×.

4. Inflammation

4.1. Overshooting Inflammation in the Kidney

Resident and infiltrating mononuclear phagocytes express the entire spectrum of innate pattern recognition receptors that translate danger recognition into a rapid inflammatory response [62,63]. In contrast, renal parenchymal cells, i.e., mesangial cells, endothelial cells, podocytes, tubular cells, and fibroblasts express only a limited spectrum of such receptors [64,65]. For example, they lack some of the endosomal nucleic acid-specific Toll-like receptors, and do not produce IL-1beta upon activation of the NLRP3 inflammasome, even though they easily get activated by bacterial endotoxin or other PAMPs and DAMPs [66,67]. This mechanism can explain how systemic or extrarenal infections can cause flares of pre-existing and smoldering forms of renal inflammation, e.g., chronic glomerulonephritis or renal vasculitis. We had addressed this concept by transiently injecting agonists to several pattern recognition receptors in mice with experimental immune complex glomerulonephritis, which then triggered the intrarenal production of cytokines, type I interferons, which increases inflammation and tissue damage [65,68–77]. PAMP-mediated renal inflammation induces the loss of renal parenchymal cells, especially podocytes [78,79], because these cannot be easily regenerated [80]. For example, mice with Alport nephropathy transiently exposed to bacterial CpG-DNA, display a transient activation of resident dendritic cells and infiltrating Ly6Chigh+ macrophages that produce pro-inflammatory mediators such as TNF, which triggered podocyte loss and thereby accelerated proteinuria and glomerular scarring [78].

In lupus nephritis, endogenous nucleic acids drive immunity in a similar manner [81,82]. Nuclear particles that contain immunostimulatory endogenous RNA and/or DNA activate antigen-presenting dendritic cells, macrophages, and B cells, to mature and to release numerous pro-inflammatory
mediators including type I interferon [82–84]. The latter sets off a coordinated antiviral immune response explaining the similarities between the clinical manifestations of viral infections and systemic lupus [85]. This process also occurs inside the kidney, as documented by the antiviral gene expression signature in renal biopsies [86,87]. For example, mesangial cells and glomerular endothelial cells use their cytosolic nucleic acid sensors to translate nucleic acid recognition into the release of type I interferons, which contribute to renal inflammation and tissue damage [88–93].

Tissue necrosis is associated with a release of endogenous ligands to pattern recognition receptors [64,94,95]. For example, postischemic tubular cell necrosis releases HMGB1 and histones that ligate TLR2 and TLR4, which trigger an acute intrarenal inflammatory response that determines the extent of AKI [66,95–99]. In addition, Tamm-Horsfall protein/uromodulin, a kidney-specific protein exclusively expressed within the distal tubule, acts as a TLR4 and NLRP3 agonists when tubular injury allows its leakage into the renal interstitium [100,101]. TLR signaling occurs in renal parenchymal cells [64] and is tightly regulated in the intrarenal network of dendritic cells by the constitutive and induced expression of several inhibitory molecules that are absent or dysfunctional in tubular epithelial cells [102–108]. In contrast, the NLRP3 inflammasome enhances tubulointerstitial but not to glomerular inflammation [19,109–111], because activated glomerular cells do not induce pro-IL-1β [110].

Figure 3. Interstitial nephritis in polyoma (BK) virus nephropathy. Local activation of inflammation can destroy renal parenchyma and cause acute kidney injury. In this example of BK virus reactivation in a kidney allograft was proven by immunostaining for BK viral protein with positivity in affected tubular epithelial cells (right). Viral replication activates antiviral immunity and immunopathology as evidenced by the dense leukocyte infiltrates in the renal interstitium (left). Original magnification 200×.

Triggered by the local release of chemokines, various subsets of leukocytes sequentially recruit into the kidney [112–120]. Macrophages, T cells, and B cells polarize into functionally distinct subsets that differently affect renal pathology [62,114,121–125]. PAMPs and DAMPs turn non-activated intrarenal and circulating mononuclear phagocytes into cells that promote immunopathology [126–128]. Blocking the CC-chemokine CCL2, or its receptor CCR2, prevents the recruitment and expansion of such classically-activated macrophages, and thereby reduces renal immunopathology in glomeruli and the tubulointerstitium, but it does not affect alternatively-activated macrophages [129–137]. Together,
the kidney is mostly affected by renal inflammation that is triggered by extrarenal infections that release immunostimulatory PAMPs into the circulation, or by intrarenal release of DAMPs that promote a sterile inflammatory response [138,139]. These immunostimulatory molecules promote unnecessary (collateral) damage to renal cells (Figure 3).

Thus, suppressing renal inflammation appears as an important strategy to preserve renal tissue, especially those epithelial cells that cannot be easily regenerated. Anti-inflammatory drugs that do not elicit systemic immunosuppressive effects hold new promise for that [140].

4.2. Insufficient Inflammation in the Kidney

While TLR-mediated renal inflammation contributes to inappropriate renal immunopathology in sterile nephropathies, it remains an important element of pathogen control in renal infections [66,141]. For example, some degree of innate immune activation is needed to keep BK virus in check to avoid viral replication and BK virus infection of the allograft [142,143]. The enigmatic importance of renal inflammation as part of the local host defense becomes evident also during bacterial pyelonephritis [144]. Intrarenal host defense is needed to limit pathogen growth and spreading to systemic infections, which happens in TLR4-mutant mice inoculated with uropathogenic *E. coli*. While these mice are protected from renal abscess formation [145], this occurs at the price of insufficient pathogen control at the entry site and could cause fatal gram negative sepsis [14]. In addition, TLR2 is required for the recognition of leptospiral outer membrane proteins in proximal tubular epithelial cells [146].

5. Epithelial Regeneration

Epithelial cells determine most of the kidney’s functions, in the glomerular compartment (filtration barrier) as well as the tubular compartment of the kidney (reabsorption and secretion). Transient and short-term injuries to the tubules are usually followed by sufficient epithelial regeneration that rapidly restores renal function [147,148]. Numerous growth factors such as HGF, PDFG, EGF, and BMP-7 drive the repair of the epithelial monolayers after injury [7,25,31,149]. In addition, the cell cycle regulator murine double minute (MDM)-2 assures cell cycle entry of surviving tubular cells by inhibiting p53-dependent cell cycle arrest [150], in addition to its role in NF-κB signaling [150,151]. Epithelial regeneration becomes effective only after the resolution of inflammation [2,5,152]. Switching the phenotype of macrophages from a pro-inflammatory (M1) toward an anti-inflammatory (M2) is important in this process [122,125,153–156]. This process is associated with the release of additional growth factors that drive epithelial recovery in the kidney, including CSF-1 that enhances M2 macrophage accumulation [137,152,155–159]. However, epithelial regeneration needs to be tightly balanced to avoid renal pathology [80].

5.1. Overshooting Epithelial Regeneration in the Kidney

When epithelial (progenitor) cells get heavily activated in the absence of the necessary signals for differentiation, overshooting and maladaptive epithelial repair results in additional renal pathology [80,160,161]. In rapid progressive glomerulonephritis glomerular vascular necrosis, and
subsequent activation of the coagulation cascade, drive intense intraglomerular inflammation [162–164]. Both, epithelial injury and inflammation induce the proliferation of parietal epithelial cells without their differentiation into podocytes, which would be required for podocyte regeneration [43,161–163]. The resulting parietal epithelial cell hyperplasia generates the initial step in glomerular crescent formation and nephron loss (Figure 4). This overshooting epithelial hyperplasia does not necessarily require inflammation as a trigger. In Col4A3-deficient mice disruption of glomerular capillaries was sufficient to trigger parietal epithelial cell hyperplasia [43]. Plasma leakage seemed to be the mitogenic stimulus for these epithelial cells that normally reside, devoid of serum contact, in the urinary space [165,166].

**Figure 4.** Overshooting epithelial regeneration in crescentic glomerulonephritis. Massive and uncoordinated proliferation of parietal epithelial cells leads to crescent formation in Bowman’s space, e.g., in necrotizing renal vasculitis. Original magnification 100×.

Epithelial hyperplasia in the tubular compartment is less obvious. The tubular progenitor cells are located at the junction of glomeruli and proximal tubules, while single progenitor cells are scattered in the proximal and distal tubules of the cortex [167,168]. Chevalier et al., have recently demonstrated that the phenomenon of atubular glomeruli originates from an obstruction of the tubular lumen by epithelial cells [169,170], a process that contributes to tip lesions in focal-segmental glomerulosclerosis and diabetic nephropathy [171,172].

5.2. Insufficient Epithelial Regeneration in the Kidney

Insufficient glomerular epithelial (podocyte) regeneration is the predominant cause for chronic kidney disease (CKD) and for progression to end stage renal disease (ESRD) (Figure 5). The particular
interaction of differentiated podocytes with each other, and with the GBM that maintains the glomerular filtration barrier remains a major obstacle for rapid repair [173–176]. This is because podocytes involve all their cytoskeleton to maintain the secondary foot processes and the slit diaphragm, which is not compatible with reorganizing the cytoskeleton to form the mitotic spindle during mitosis [177]. Thus, when podocytes enter the S phase of the cell cycle to undergo hypertrophy, cell cycle arrest at the G1 and G2/M restriction points are needed to prevent the podocyte to undergo mitosis or, otherwise, podocytes will subsequently detach and die, i.e., mitotic catastrophe [177–180]. There has been a controversial debate whether bone marrow-derived progenitors are able to replace lost podocytes [181–183], but meanwhile it has been demonstrated that podocytes originate from local epithelial progenitors at the urinary pole of the glomerulus that can migrate to the vascular pole and differentiate into terminally differentiated podocytes on the glomerular tuft [178,184,185]. This process contributes to renal development and podocyte expansion during kidney growth in early childhood [101] but its capacity to replace injured podocytes seems to be limited in adults [184,186]. The signaling pathways that regulate podocyte renewal from parietal epithelial cells remain to be clarified. Notch and Wnt signaling, EGF and SDF-1/CXCL12 seem to have a role [164,178,187,188]. Specific epigenetic imprinting at histone H3K9, H3K23 (acetylation), H3K4 (dimethylation), and H3K4 phosphorylation at serine 10, which alters gene expression and cell growth, are associated with incomplete podocyte recovery [189,190].

The persistence of classically-activated mononuclear phagocytes or repetitive/persistent triggers of kidney injury also impair epithelial repair in the tubulointerstitial compartment. CSF-1 is a mediator of this process [159]. In addition, severe kidney injury may eradicate the tubular progenitor cells that have a higher capacity to survive stress [191]. Bone marrow stem cells do not directly replace tubular cells by differentiation, but provide paracrine support to the regenerative capacity of local progenitor cells and other surviving epithelial cells [154,168,192–194]. An insufficient regeneration of injured tubular epithelial cells will lead to tubular atrophy and nephron loss, a typical characteristic of progressive CKD (Figure 5).

Together, a coordinated epithelial regeneration is needed upon injury, which first requires vascular sealing and the resolution of inflammation. Insufficient epithelial regeneration leads to atrophy and mesenchymal repair, i.e., tubular atrophy and glomerulosclerosis. Overshooting epithelial repair, i.e., hyperplasia, is another form of renal pathology, e.g., the glomerular crescent. Finding ways to enhance a coordinated proliferation and differentiation of surviving epithelial cells remains a challenge for the future.
Figure 5. Insufficient epithelial repair results in mesenchymal repair. Loss of glomerular epithelial cells (podocytes) cannot be easily repaired in adults leading to focal-segmental glomerulosclerosis (upper left). Global glomerulosclerosis (upper right) results from the progression of focal-segmental lesions or as a consequence of diffuse and persistent disease mechanisms such as diabetes, hypertension, or immune complex glomerulonephritis. Here also, mesangial cells contribute to the sclerosis by excess production of mesangial matrix. In chronic kidney disease insufficient tubular regeneration results in tubular atrophy, which is usually associated concomitant tubulointerstitial fibrosis. These complex lesions make it difficult to appreciate the individual contributing danger response programs. Magnification 100×–400×.

6. Mesenchymal Repair

Tissue healing is not limited to epithelia but also includes recovery of vasculature, tendons, fasciae, bones, and muscles, all being mesenchymal structures that contribute to function, not only of the musculoskeletal system but also to that of solid organs. For example, mesenchymal repair contributes to mechanical stabilization of organs like the lung, the heart, and the kidney, which is why epithelial growth factors are secreted together with growth factors that stimulate mesenchymal repair, e.g., by
increasing the secretion of extracellular matrix components [31]. In skin wounds, dermal fibroblasts get activated to transform into myofibroblasts that produce large amounts of type I collagen, which promotes wound contraction as a way to reduce wound size for more rapid re-epithelisation [2]. Irreversible tissue losses such as in ruptured ligaments or burned skin get filled by fibrous tissue to regain tissue stability [2]. These benefits of mesenchymal repair explain why this response program was positively selected and maintained along evolution. Solid organs like the kidney, however, often suffer from global scarring and progressive fibrosis because of the diffuse nature of the metabolic, hemodynamic, and toxic injuries that commonly affect the kidney (Figure 5). [49]. That is why it is not at all clear whether diffuse renal fibrosis is an overshooting, or simply a diffuse response. For example, interstitial fibrosis in focal-segmental glomerulosclerosis (FSGS) starts in a focal manner around those single nephrons that succumb to scarring [173]. The diffuse appearance of interstitial fibrosis only develops once many nephrons undergo the same process. The mesenchymal “repair” of each dying nephron then leads to confluent fibrotic lesions that give the impression that it is the fibrosis that accounts for renal dysfunction [46,49,173,195]. The extracellular matrix mainly replaces lost renal epithelia. As such, reducing interstitial fibrosis may result in even smaller kidneys, if not being accompanied by sufficient generation of new nephrons, a process which fish can do, but mammals cannot [196]. For the sake of didactic clarity, we will continue to use the term “overshooting” mesenchymal repair for the discussion of fibrosis as a danger response program that accounts for renal pathology.

6.1. Insufficient Mesenchymal Repair in the Kidney

Insufficient mesangial repair is a hardly known phenomenon in kidney pathology, or at least poorly defined. Mesangiolysis can be considered as a lesion of incomplete mesenchymal repair, but mesangiolysis is rarely described in renal biopsies, as it is mostly a transient phenomenon followed by rapid, (and often overshooting) mesangial cell recovery [197,198]. Mesangiolysis often results from massive renal complement activation, as in C3 glomerulopathies, atypical hemolytic uremic syndrome, or immune complex glomerulonephritis [199].

6.2. Overshooting Mesenchymal Repair in the Kidney

Mesangial repair after inflammatory injury can occur from three sources: surviving mesangial cells [198], from the extraglomerular mesangium [200], and from the bone marrow [201]. Mesangial injury rarely occurs in an isolated manner, but complicates diseases that are associated with extensive complement activation such as hemolytic uremic syndrome. The rat anti-Thy1.1 model is frequently used to study the mechanisms of mesangial repair upon mesangiolysis. Hugo et al., first reported that the hyperproliferative response upon mesangiolysis originates from surviving mesangial cells or local progenitor cells that reside in the extraglomerular mesangium [200]. Mesangial hyperproliferation also contributes to a histopathological lesion named “membrano-proliferative glomerulonephritis” where hereditary, or acquired forms, of extensive complement activation within the mesangium lead to a persistent expansion of mesangial cells that even extend into the space between the GBM and the endothelial cells [202]. The mesangial matrix produced along these mesangial cell extensions stains
positive with silver, which then gives glomerular capillaries a splitted GBM appearance on light microscopy [202].

In the glomerulus this causal relationship becomes clear, as podocyte renewal from local progenitors is mostly insufficient, especially in proteinuric disorders of the adult [80,203]. In FSGS, parietal epithelial cells rather produce extracellular matrix, and generate segmental sclerotic lesions, than regenerating lost podocytes [204]. This focal synchia has still the potential to stabilize the focal loss of podocytes as in some forms of secondary FSGS [171]. However, beyond a certain amount of lost podocytes, the scarring process acquires its own dynamic and progresses to global glomerulosclerosis [175], because hyperfiltration of the remaining glomerulus adds more hemodynamic stress on the surviving podocytes [173,205]. The mesenchymal transition of parietal epithelial cells further contributes to fibrocellular crescent formation, implying an irreversible loss of the entire nephron [206]. In this way, parietal epithelial cells directly contribute, not only to epithelial, but also to mesenchymal repair [166].

The process of epithelial-mesenchymal transition of surviving epithelial cells that cannot rapidly regenerate epithelial injuries has attracted a lot of attention [46,207–209]. It is based on the observation that epithelial cells of mesenchymal origin, like the renal epithelia, re-express mesenchymal markers upon injury in vitro and in vivo [46]. This has led to the assumption that such cells could leave tubular compartment and migrate into the renal interstitium where they may fuel into the heterogeneous pool of fibroblasts and contribute extracellular matrix production and fibrotic lesions [46,49]. The significance of this phenomenon for human kidney disease remains under debate because clear evidence for tubular cells leaving the tubular compartment in vivo is still lacking [46,207–209]. In the glomerulus, however, parietal epithelial cells that do not adequately differentiate into podocytes clearly undergo this mesenchymal transition and cause scarring, as there is no need for them to leave their home compartment (Figure 5) [43,206].

The concept that renal interstitial fibrosis accounts for renal dysfunction originates from the close association of the extent of renal fibrosis with poor outcomes of primary glomerular disorders [210], but functional studies do not always support this causal relationship [49,196]. It is of note that the driving factor of interstitial fibrosis seems to be epithelial injury and insufficient epithelial repair [211], e.g., when proliferating epithelial cells get arrested in the G2/M phase and start to produce tumor growth factor-beta [44]. This process is also triggered by aristocholic acid [44,212], the nephrotoxic element of Chinese herb nephropathy [213]. Bone marrow progenitor cells and leukocytes enhance the process of renal fibrosis, as evidenced by experimental interventions that block leukocyte recruitment and can prevent interstitial fibrosis either as a direct or an indirect effect [112,134,214–219]. For example, inhibition, genetic deletion, or depletion of alternatively-activated (M2) macrophages protects from renal fibrosis [122,155,156,220–227]. Fibrocytes are a particular type of Ly6G+ collagen-producing cell that originate from myeloid precursors in the bone marrow and that recruit to sites of chronic kidney injury [228,229]. Ly6G+ fibrocytes specifically recruit via CCL21-CCR7 and not via CCL2-CCR2 like pro-inflammatory macrophages, but once they reach the kidney they contribute to local collagen deposition and interstitial fibrosis [230,231].

Vascular reconstruction is another element of mesenchymal healing [232]. Pericytes stabilize microvessels not only during homeostasis, but also during microvessel recovery, a process mediated
by TIMP3 and ADAMTS1 [233]. Their capacity to produce collagen adds pericytes to the list of cells that contribute to renal interstitial fibrosis and sclerosis [234].

Together, mesenchymal repair is needed to stabilize and rebuild tissues after injury, especially after loss of parenchymal tissue. Insufficient scarring is rarely a problem in the kidney. In contrast, scarring within the glomerulus, usually upon dysregulated epithelial repair like in podocyte loss, or crescent formation, is the greatest concern as FSGS and fibrocellular crescents both eventually lead to loss of the entire nephron (Figure 5). Within the interstitial compartment fibroblast- and pericyte-derived extracellular matrix fills the gaps left by dying nephrons and, this way, stabilizes the remaining nephrons. This process, however, further contributes to vascular rarefication and renal ischemia and is thought to further promote the progression of kidney disease. Hence, an otherwise beneficial wound healing response turns into a maladaptive process that promotes organ failure, mainly because of the diffuse nature of most kidney diseases.

7. Summary

Clotting, inflammation, epithelial, and mesenchymal healing represent ancient danger response mechanisms that were positively selected throughout evolution for their benefits on host survival upon focal injury. In focal injuries the associated collateral damages may be acceptable. In contrast, in diffuse injuries, as they usually affect the kidney, these danger response programs often turn into maladaptive pathomechanisms that account for organ failure. Research efforts can benefit from dissecting these individual danger response programs, and from studying their regulatory interactions. From a therapeutic perspective, inhibiting the unnecessary inflammatory response in renal sterile inflammation and stimulating a coordinated epithelial repair should be the most promising strategies to avoid kidney pathology and disease progression.

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Conflict of Interest

The authors declare no conflict of interest.

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