Molecular mechanisms of postintensive care syndrome

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Effectiveness of intensive care must be evaluated not only by short-term survival after a critical illness, but also by the recovery to an adequate quality of life. The increased evidence of long-term functional disabilities in intensive care survivors led to the definition of post-intensive care syndrome (PICS) [1]. Early diagnosis and effective treatments for these newly recognized conditions are warranted. However, most of the initial efforts to limit long-term sequelae have not yielded satisfactory results [2]. The objective of this review is to identify the molecular mechanisms that lead to organ dysfunction after intensive care and to summarize them into several plausible unifying hypotheses. From these mechanisms, novel therapeutic targets with the potential to prevent PICS may arise [3], allowing for earlier interventions during acute organ failure aimed to improve the quality of life of intensive care unit (ICU) survivors. Cost-effective strategies based on growing pathogenetic evidence on PICS would hence allocate research efforts and funding to implement preventive treatments, to impede pathogenetic mechanisms triggered during ICU stay, rather than exclusively rehabilitate long-term sequelae when they are already established.

The spectrum of postintensive care syndrome

The improvement of mortality rates in the ICU has evidenced that survivors to a critical illness face a number of long-term severe complications and sequelae that can impair their quality of life [4]. Several factors, including the population aging along with the emergence of invasive therapies that may improve the outcomes, have increased the interest in these long-term conditions [5]. An expert panel in 2012 defined PICS as the “new or worsening impairments in physical, cognitive or mental health status arising after critical illness and persisting beyond acute care hospitalization” [1]. It must be noted that this definition provides a framework to improve awareness, research and diagnostic and therapeutic approaches, rather to define a classical syndrome [6].

PICS covers several dimensions, including physical, cognitive and emotional aspects (Fig. 1), for many of which there is no standard definition or diagnostic criteria. Long-term respiratory sequelae include impairments in lung volumes, ventilatory dynamics and diffusion [7]. Although some studies report a mild impairment...
in most of the cases, the recent COVID-19 pandemic has highlighted the relevance of the long-term, post-acute respiratory distress syndrome (ARDS) respiratory sequelae [8]. Musculoskeletal impairments are included under the concept of “ICU-acquired weakness” (ICUAW), defined as a “diffuse, symmetric, generalized muscle weakness, detected by physical examination and meeting specific strength related criteria) that develops after the onset of critical illness without other identifiable cause”. ICUAW may result in a severe limitation of daily activities and a significant worsening in quality of life. Although some improvements may occur during the first year after ICU discharge, weakness is persistent in a significant proportion of cases [9]. Finally, neuropsychological alterations regarding cognitive declines in ICU survivors have been also described by several authors. Up to 80% of critically ill patients experience delirium while in the ICU, and a significant number of ICU survivors show signs of moderate cognitive impairment or other neurological, emotional and mental health conditions related to PICS include depression, anxiety, post-traumatic stress disorder and cognitive impairment [10, 11]. Again, these disarrangements may persist well above the first year and cause a severe limitation of patients’ activities.

Several ICU-related risk factors and short-term complications have been related to these long-term outcomes (highlighted in Fig. 1). However, as pathogenetic factors are mostly unknown, it is not clear if these short- and long-term symptoms are time-dependent manifestations of a common disease, independent diseases with shared etiologies or independent sequelae caused by the systemic response to a severe injury.
Mechanisms of chronic lung dysfunction

The need of respiratory support is one of the main reasons for ICU admission, either due to lung injury or ventilatory failure. These critically ill patients often require mechanical ventilation. Previous organ damage, along with the use of ventilation, may lead to the development or worsening of lung injury [12], which involves epithelial barrier dysfunction, inflammation and matrix remodelling. In this context, failure to correctly resolve these processes might be involved in the development of long-term sequelae. However, the specific mechanisms by which acute lung damage becomes chronic are yet to be fully elucidated. Most of the knowledge on this topic comes from research on prevalent chronic lung diseases, such as idiopathic pulmonary fibrosis, which may hint to underlying pathogenetic mechanisms. These same processes may play a role in the development of chronic lung dysfunction in the context of post-ICU sequelae (Fig. 2).

Inflammation and matrix remodelling are well described processes involved in the resolution of acute lung injury [13]. However, their perpetuation can be a relevant pathogenetic mechanism of many chronic lung diseases [14]. Persistence of the local inflammatory response has been linked to the development of fibrosis, as released Th2 cytokines (IL-4, -5, -13) have a well-known pro-fibrotic effect and may recruit fibrocytes from the systemic circulation. Moreover, other pro-inflammatory mediators such as IL-1b or IL-6 may promote collagen deposition mediated by IL-17 [15].

In this setting, alveolar macrophages, inflammatory cells and fibroblasts release profibrotic molecules during acute injury, such as transforming growth factor-β (TGFβ), Insulin-like growth factor (IGF-1), platelet derived growth factor (PDGF) or connective tissue growth factor (CTGF) among others [16–19]. TGFβ activates intracellular SMAD complexes via binding to serine/threonine kinase heterodimers in the cell surface. Activated SMAD complexes enter the nucleus and act as...
transcription factors regulating a wide range of cellular processes. In fibrosis, these pathways include extracellular matrix deposition and fibroblast division and differentiation into myofibroblasts [20]. These cells, characterized by an increase in the intracellular content of α-smooth muscle actin (α-SMA), modify the matrix composition by increasing deposition of collagen and disorganizing elastin, generating scar-like lesions [21].

Activation of coagulation and fibrin deposition is another pathogenetic mechanism activated during acute lung injury that has been linked to long-term sequelae. It has been shown that patients with lung interstitial diseases have an increased expression of procoagulant factors within the lung, including tissue factor or thrombin, or a decrease in protein C. Activation of proteinase-activated receptors (PARs) by the proteinases from the coagulation cascade (thrombin, trypsin, cathepsins...) provides the mechanistic link between coagulation and fibrosis. Downstream signaling following PAR1 activation results in the expression of several profibrotic growth factors (CTFG, PDGF) and perpetuates the local release of proinflammatory cytokines and TGFβ [22].

Epithelial–Mesenchymal Transition (EMT) has also gained relevance in this scenario, where massive tissue remodeling takes place. EMT is a process in which a polarized epithelial cell acquires a mesenchymal phenotype, that includes synthesis of extracellular matrix components [23]. During EMT, epithelial cells lose part of the epithelial characteristics, such as expression of E-cadherin and cytokeratin, and gain mesenchymal markers including N-cadherin, vimentin or α-smooth muscle actin [24]. At a physiological level, all these processes favour the accumulation of excessive fibrous tissue, decreasing lung compliance and impairing ventilatory dynamics and diffusion. In vivo models of lung injury and mechanical ventilation have shown the activation of EMT, possibly by a Wnt-dependent mechanism [25], suggesting a relationship between EMT-like processes and the later development of pulmonary fibrosis [26].

Another common feature in these chronic conditions is epithelial barrier dysfunction, characterized by altered cell composition of the pseudostratified respiratory epithelium with basal and goblet cell hyperplasia and metaplasia [27, 28]. In addition, after the initial lung insult, persistence of epithelial dysfunction is associated with a proinflammatory secretory phenotype due to the activation of airway epithelial cells, dendritic cells and type 2 Innate Lymphoid Cells, and release of epithelial derived cytokines, including thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33 [29]. The resulting sustained inflammation and shift in cellular composition could play an important role in post-ICU lung dysfunction.

Finally, cell renewal is a key feature of chronic lung diseases. Excessive stem cell activation leads to accumulation of DNA damage and cell senescence [30]. In patients with idiopathic pulmonary fibrosis, epithelial cells show an increase expression of senescence markers, such as P16 or P21 and a proinflammatory phenotype [31]. Recently, we have shown the activation of this pathway in response to acute lung injury [32]. These senescent cells have been related to stem cell exhaustion with an impaired regenerative capacity [33] and an increased secretion of inflammatory and matrix remodeling molecules, which in turn may perpetuate fibrosis.
Molecular mechanisms of cognitive impairment

There are several mechanisms that may lead to brain injury in critically ill patients [34]. The central nervous system (CNS) receives signals from neural afferences and circulating factors and cells. Regarding the former, the vagus nerve constitutes the main ascending pathway from peripheral organs. Distal vagal sensors are responsive to a variety of stimuli, including stretch (via transient receptor potential cation channel, subfamily V, member 4 [TRPV4] and Piezo receptors) [35], or inflammation (via toll-like receptor (TLR)-4, IL1R or tumor necrosis factor [TNF]-receptor present in vagal sensory neurons) [36, 37]. Once these signals reach the brain stem, multisynaptic pathways along the CNS are activated [38, 39]. For instance, lung stretch activates alveolar TRPV4 and purinergic receptors, that, in a vagus-dependent manner, increase dopaminergic signaling and triggers hippocampal apoptosis [40]. Blockade of triggering receptors in distal organs or circulating mediators could decrease the risk of long-term impairment. In animal models, inhibition of peripheral mechanosensation with TRPV4 antagonists, unspecific blockade of nerve conduction with lidocaine or inhibition of type 2 dopamine receptors have decreased hippocampal apoptosis [35].

Circulating molecules and cells may also reach the brain during critical illness. The systemic inflammatory response decreases blood–brain barrier permeability [41] and facilitates the translocation of circulating mediators and/or cells that further promote brain injury. Heparan sulfate fragments released from the endothelial glicocalix during sepsis may translocate to the hippocampus and inhibit brain-derived neurotrophic factor signaling, that results in memory impairment in mice [42]. Circulating IL-6 may also play a role in this setting, as peripheral blockade of IL-6 with a monoclonal antibody prevented ventilator-induced brain injury [43]. In line with these findings, intratracheal instillation of lipopolysaccharide increases the expression of proinflammatory cytokines Il1b and Il6 in the brain stem [44]. Interestingly, only the increase in Il1b expression was abolished after vagotomy, suggesting the simultaneous activation of different mechanisms.

The link between these brain responses and functional outcomes has also been assessed. In a large animal model of prolonged protective mechanical ventilation, hippocampal damage was demonstrated [45]. Acute lung damage and mechanical ventilation in mice caused brain inflammation, hippocampal injury and memory impairments, in an steroid-preventable manner [41]. Similarly, conditioning responses, a surrogate marker of memory in mice, were absent 3 days after mechanical ventilation, but not in anesthetized, non-ventilated controls [46]. Although translation of these experimental results into clinical evidence is challenging and remains elusive, this model of brain injury in response to systemic insults (summarized in Fig. 3) provides a framework for prevention, diagnosis and treatment of long-term cognitive dysfunction in critically ill patients.

Mechanisms of ICU-acquired weakness

ICUAW is a bilateral and symmetrical neuromuscular involvement, common in critically ill mechanically ventilated patients. Clinical studies in critical care settings involving electrophysiological tests and muscle histopathology suggest that both polyneuropathy and myopathy may coexist in ICU patients, being myopathy more
frequently identified as the cause of weakness [47]. Critical illness neuropathy has been described as a distal axonal sensory-motor polyneuropathy affecting limb and respiratory muscles. Some evidence suggests that weakness recovery could be worsened and/or delayed when neuropathy accompanies myopathy, being persisting disability associated with polyneuropathy and myopathy coexistence [48, 49]. Because nerve conduction studies and needle electromyography do not accurately discern between both entities, and given the sufficiently relevant clinical problem of muscle weakness in these patients [50], the term ICUAW emerged regardless of its causative nature. Although physical disability related to ICUAW is highly prevalent among ICU survivors, its clinical spectrum varies not only in severity but also in recovery trajectories [51]. Muscle atrophy in the critically-ill has been demonstrated to begin within the first hours after ICU admission in mechanically ventilated patients [52] and its development has been related to several factors, such as systemic inflammation, severity of the underlying disease, use of neuromuscular blockers or mechanical ventilation itself [49, 53, 54].

Multiple molecular mechanisms, either independent or interacting, are involved in muscle wasting and evolve over time, from the onset of critical illness till the long-term recovery phase around 6 months after ICU discharge [55] (Fig. 4). Muscle

![Fig. 3](#)  
*Fig. 3* Mechanisms of brain damage after critical illness. Neural and circulating signals reach the brain during critical illness and trigger several pathogenetic responses, including neuronal apoptosis, cell activation and amyloid deposition, that could explain the long-term sequelae experienced by ICU survivors.
wasting results from an increased proteolysis triggered in the acute phase, overwhelming the regenerative capacity of the injured tissue [52, 56]. Early activation of proteolytic pathways, however, is not sustained over time, but instead it may alter muscle biology resulting in an impaired muscle regrowth [57].

Inflammatory cytokines have been suggested to play a relevant role in the development of ICUAW. TNFα has been widely studied in this setting. In differentiated myotubes, TNFα stimulates catabolism by binding to TNF receptor subtype 1 and activating nuclear factor-kB. This transcriptional factor is essential for TNFα-induced reduction in muscle protein and loss of adult myosin heavy chain content [58], which is specifically found in critically ill patients [59]. This pathway is also sensitive to reactive oxygen species, which appear to function as second messengers for TNFα in skeletal muscle [58]. TNFα/nuclear factor-kB signaling is also involved in the differentiation process, representing a mechanism that could be responsible for satellite cells activation and skeletal muscle feedback.
muscle recovery following the acute phase [60–62]. TNFα binding to its receptor also stimulates apoptosis and Jun-N-terminal kinases and mitogen-activated protein kinases (MAPKs) in differentiated myotubes. In muscle cells, these signaling events stimulate the expression of genes related to the ubiquitin–proteasome pathway [63, 64], triggering massive intracellular proteolysis [65]. Finally, TNFα is also known to affect the force of muscle contraction even in the absence of atrophy [66] via TNFR1 and mediated by an increased cytosolic oxidant activity [67, 68].

Elevated levels of IL-1 are commonly found in critically ill patients’ serum and represent a potential stimulus for protein loss and muscle atrophy. The suggested underlying mechanisms are related to both protein synthesis and degradation [69, 70]. Interestingly, IL-6 has been proven to drive the systemic compensatory anti-inflammatory response syndrome, by inhibiting TNFα release and stimulating IL-10 [71]. In skeletal muscle, IL-6 is involved in myogenesis, lipid metabolism, glucose uptake and both protein synthesis and degradation [72–74]. Skeletal muscle cellular niche has been recognized itself as a myokine secretor organ and even a potential regulator of immune system [75]. In mechanically ventilated patients who developed myopathy, the inflammation-induced acute phase response resulted in a marked increase in IL-6 production in skeletal muscle [76].

Histologic and molecular analyses performed in skeletal muscle biopsies of critically ill patients suggest that recovery failure may be associated with satellite/progenitor cells loss and fibrosis [57], but it is unclear which are the underlying mechanisms leading to the satellite cell depletion or what is the role of the whole skeletal muscle cell niche. In other scenarios, where muscle injury may occur, muscle tissue repair is a complex biological process that necessarily involves activation of stem cells. Myogenic stem cells, so-called satellite cells, reside beneath the basal lamina of muscle fibers [77] and express both NCAM/CD56 and early myogenic cell markers, such as M-cadherin, PAX7, and MYF5 [78]. Satellite cells remain quiescent in skeletal muscle, but they can proliferate and further differentiate into myoblasts in response to activating signals, achieving muscle regeneration [79]. Activated satellite cells may interact with macrophages recruited at the site of muscle regeneration and receive mitogenic signals from these immune cells, mediated by the release of different soluble factors [80]. Myoblasts, and to a higher extent myotubes, also receive cell-contact-mediated pro-survival signals from macrophages [81].

Similarly, the microvascular niche seems to be another partner of satellite cells. Christov et al. have suggested quiescent satellite cells to easily interplay with endothelial cells upon activation to set up coordinated angio-myogenesis in a functional manner [82]. Indeed, angiogenesis and myogenesis could share regulatory factors such as vascular endothelial growth factor (VEGF) [83] or insulin-like growth factor type 1 (IGF1) [84] that reciprocally signal both processes pivotaly involved in muscle regeneration. Apart from inflammation and stem cell depletion, several other mechanisms may be involved in the development of persistent muscle weakness in survivors of critical illness. Distal axonal sensory-motor damage/dysfunction has also been described in ICUAW, being attributable to a reduced membrane excitability resulting from membrane depolarization and ion channel dysfunction [85, 86], together with an altered calcium homeostasis [87]. In critically-ill patients with demonstrated polyneuropathy, motor axons are
depolarized. Chronic membrane depolarization could be related to tissue hypoperfusion or to increased extracellular potassium in patients with kidney failure, and may lead to muscle atrophy [88]. Reduced compound motor action potentials are present in neuropathy and myopathy. In addition, there have been described fibrillation potentials or positive sharp waves that could be explained by denervation or by muscle sodium channel dysfunction [89]. Mitochondrial dysfunction could be a contributing defect involved in energy-dependent processes [90], and a dysregulation in autophagy [91] has also been described to play a role in muscle repair.

In critically ill patients, the limited sample size of the muscle specimens precludes the identification of different mechanism-specific subphenotypes of muscle weakness, with different histopathological findings and driven by different mechanisms, though leading to the wide clinical spectrum of long-term functional disability. These different pathogenetic subphenotypes could explain the heterogeneous recovery observed among survivors of critical illness. For instance, the activated pathways could be promoting proliferation of satellite cells in some patients while related to fibrotic repair and satellite cell depletion in others. Understanding these mechanisms is crucial to identify therapeutic targets that, interfered at the beginning of the process, could modify the clinical course of ICUAW before the 6-month plateau has been achieved, either at the acute phase or during recovery.

Unifying hypotheses

Long-term sequelae included in the PICS framework may be the consequence of organ-specific mechanisms, as described in the previous sections. However, the variety of symptoms included in PICS in response to common triggers (the critical disease and its managements) and the observed links and correlations amongst the different dimensions of the syndrome [92] raise the hypothesis that PICS is the long-term result of underlying mechanisms activated by severe diseases, that become systemic and lead to different degrees of multi-organ dysfunction. There are several stereotypical biological responses and mechanisms that could be involved in the development of PICS. Identification of these shared mechanisms could help to identify patients at risk of developing sequelae. Moreover, this knowledge could lead to novel therapeutic interventions that might prevent the whole spectrum of PICS by interfering with upstream regulators.

Systemic inflammation

The most characterized and studied mechanism in this setting is the inflammatory response. Inflammation is a physiological response necessary to fight against infections or injury and, therefore, restore homeostasis. During the acute phase of the inflammatory response, the presence of damage or pathogen-associated molecular patterns (DAMPs and PAMPs respectively) induces an initial systemic inflammatory response, mediated by the release of pro-inflammatory mediators, such as growth factors (i.e., G/GM-CSF, FltL) and cytokines (i.e., IL-1, IL-6, IL-17) as well as through mesenchymal or immune cells [93]. This coexists with a compensatory anti-inflammatory response syndrome, which is mainly carried out by myeloid suppressor cells (MDSCs) that secrete anti-inflammatory cytokines (e.g., IL-10 and TGFβ) and cytokine antagonists (e.g.,
IL-1ra and sTNFRI) and decrease inflammation without eliminating all protective innate immunity [94].

During chronic inflammation, an unbalance between pro- and anti-inflammatory mediators makes homeostasis impossible to restore. The persistence of stimuli that modify the inflammatory response, either directly or indirectly, may perpetuate the release of inflammatory mediators not only to the lung but also to the systemic compartment, as the increased alveolo-capillary permeability facilitates their translocation. This persistent inflammation has been demonstrated in ARDS survivors even after clinical improvement or recover and related to worse physical recovery [95].

Senescence
Other potential mechanism which might be involved in PICS is related to the activation and spread of senescent responses. Cell senescence is defined as the cell cycle arrest in response to a stimulus, and a shift towards a specific phenotype characterized by the loss of several cell functions and the paracrine release of a variety of molecules (termed senescence-associated secretory phenotype—SASP), including proinflammatory mediators and senescence inductors (thus activating a positive feedback) [96]. There are several molecular pathways that lead to senescence in response to injury (including oxidative stress, release of DAMPs, proinflammatory cytokines, such as TNFα or IL-1α), most of which depend on the activation of P53, P21 and their downstream factors [97]. In a model of acute lung injury, we demonstrated that activation of these pathways results in short-term protection against apoptosis (as senescent cells have an inherent resistance to programmed cell death) [32, 98]. However, the resulting senescent state could lead to long-term sequelae, both locally and in distant organs (in response to SASP). Several of the previously described mechanisms of organ-specific PICS could be manifestation of these senescent responses. Senescence is an emerging pathogenetic pathway in idiopathic lung fibrosis [31], but their involvement in secondary fibrosis is unknown. Several forms of acute lung injury can trigger senescence in response to DNA damage. The previously described satellite cell exhaustion in ICUAW could be also a manifestation of the systemic release of pro-senescent factors. Recently, it has been described the deposition of brain amyloid fibers, a known trigger of neuronal senescence, in response to critical illness [99].

Of note, there is a positive feedback between inflammation and senescence. Inflammation causes activation of senescence through several mediators, such as IL-6. In turn, SASP includes the release of proinflammatory molecules, thus promoting a sustained response [100].

Integrated stress response
A third mechanism potentially involved in the development of PICS is the so-called integrated stress response (ISR). ISR is a conserved cell response to different pathological conditions that results in a general decrease in protein synthesis and expression of a specific gene signature. Its activation is necessary to maintain cell homeostasis in the presence of different stress signals [101]. This response may be activated by four stress-sensing kinases (protein kinase R [PKR], Eukaryotic translation initiation factor 2-alpha kinase 4 [EIF2AK4], heme-regulated inhibitor [HRI] and PKR-like endoplasmic
reticulum kinase [PERK]) that phosphorylate the eukaryotic initiation factor eIF2α, which ultimately leads to a decrease in protein synthesis and the induction of selected genes (such as ATF4 and CHOP) that eventually take part in the cellular response to stress.

ISR plays an important role during acute lung injury or mechanical ventilation. Alveolar overdistension induced by mechanical ventilation results in PERK phosphorylation and subsequent phosphorylation of the factor eIF2α. This alters epithelial permeability, induces proinflammatory cytokine release and cell death [102]. ISR may have a dual role deciding cell fate. Although its main function is maintaining cell survival, exposure to a continuous stress could lead to cell death [103]. In this context, the stress-inducible phosphatase GADD34 dephosphorylates eIF2α and induces a negative feedback mechanism, ceasing the activation of ISR [104]. However, in pathological conditions, ISR is activated but GADD34 expression is attenuated, thus preserving phosphorylated eIF2α [105] and perpetuating this response [106] due to the lack of negative feedback.

From common triggers to cellular and tissue dysfunction

Finally, all these pathways converge in a reduced number of cell responses that mediate tissue dysfunction. The most studied response is apoptosis. There is substantial evidence showing disseminated apoptosis during the acute response to critical illness [107]. This programmed cell death is activated by binding of extracellular signaling molecules (i.e., TNFα) to membrane receptors or intracellular release of cytochrome c from injured mitochondria (i.e., after oxidative stress). These pathways converge in the activation of caspases, that lead to DNA fragmentation and cell death. Although apoptosis is a major pathogenetic mechanism in acute organ failure, and anti-apoptotic drugs may prevent organ damage in this setting, the relationship of acute apoptosis and development of PICS remains to be fully elucidated. Animal models have shown a correlation between apoptosis and later development of pulmonary fibrosis [108] and neurological deficits [46], but human data is scarce. Patients with ICUAW show activation of proapoptotic pathways in peripheral muscles [109].

Activation of senescence, that render cells resistant to apoptosis [110], may be a compensatory mechanism in this setting, but at the price of the promoting persistence of senescent, dysfunctional cells. Senolytics, a heterogeneous family of compounds that inhibit pro-survival kinases in senescent cells (such as BCL2 or tyrosine-kinases), may promote the selective death of these cells, facilitating a delayed repair [111]. Although promising, these pathways have not been explored in critically ill patients.

Emerging PICS domains

Rather than a settled syndromic condition, PICS is an evolving concept that covers a large variety of symptoms and conditions experienced by ICU survivors. Clinical research in this topic may help to better identify, characterize and manage the long-term consequences of critical illness from the early onset of acute illnesses. The main components of PICS have been covered in the previous sections, but the systemic nature of acute severe diseases may cause other organ injuries.

Critical illness may increase the risk of cardiovascular events after ICU and hospital discharge. Greater rates of atrial fibrillation, heart failure, and myocardial infarction
have been described after sepsis [112]. However, no clear organ-specific mechanisms have been identified to date [113]. Systemic persistent inflammation is a major driver of cardiovascular disease, but a clear causative link is missing [114]. Recently, the role of stress-triggered senescence has been highlighted in this setting [115].

Similarly, there is increasing evidence of long-term impaired kidney function after critical care, even in patients without acute renal failure [116]. The development of kidney fibrosis during the repair phase has been proposed as a major pathogenetic mechanism [117]. In addition, cell cycle arrest, a hallmark of senescence, promotes fibrosis during kidney repair [118]. The previously described cardiovascular impairment could contribute to further deteriorate kidney function.

Finally, transgenerational effects of critical illness, requiring modification of the genome or epigenome of germline cells, have barely been explored. It has been shown that experimental sepsis changes the sperm methylome, mainly in intergenic regions or development-related genes [119]. Both systemic and local inflammation can modify the expression of methyltransferases and thus facilitate cell reprogramming. The consequences of these changes in offspring, however, are controversial [120]. Besides, maternal prenatal exposures in human studies have focused on pregnancy, rarely assessing long term effects of exposures of maternal non-pregnant progenitor in later offspring [121].

Conclusions
The objectives of intensive care must go well beyond ICU survival and aim to provide critically ill patients with the best achievable quality of life. This includes prevention, treatment and/or palliation of the long-term sequels derived from their ICU stay. The complex organ crosstalk and the pleiotropic effects of most of the responses triggered by critical illness make difficult to find treatments that translate into a clinical benefit. In this difficult scenario, knowledge of the underlying biological mechanisms may allow clinicians and researchers to identify novel biomarkers, therapeutic targets and strategies that ultimately will facilitate the identification and treatment of these long-term sequelae even at early and acute stages, thus contributing to improve long-term outcomes.

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References
1. Needham DM, Davidson J, Cohen H et al (2012) Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders’ conference. Crit Care Med 40:502–509. https://doi.org/10.1097/CCM.0b013e318232da75
2. Brown SM, Bose S, Banner-Goodspeed V et al (2019) Approaches to addressing post-intensive care syndrome among intensive care unit survivors. a narrative review. Ann Am Thorac Soc 16:947–956. https://doi.org/10.1513/AnnalsATS.201812-913FR
3. Juffermans NP, Radermacher P, Laffey JG, Translational Biology Group (2020) The importance of discovery science in the development of therapies for the critically ill. Intensive Care Med Exp 8:17. https://doi.org/10.1186/s40635-020-00304-4
4. Herridge MS, Tansey CM, Matté A et al (2011) Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 364:1293–1304. https://doi.org/10.1056/NEJMoa1018022
5. Bottom-Tanzer SF, Poyant JO, Louzada MT et al (2021) High occurrence of postintensive care syndrome identified in surgical ICU survivors after implementation of a multidisciplinary clinic. J Trauma Acute Care Surg 91:406–412. https://doi.org/10.1097/TA.0000000000003231
6. Rousseau A-F, Prescott HC, Brett SJ et al (2021) Long-term outcomes after critical illness: recent insights. Crit Care 25:108. https://doi.org/10.1186/s13054-021-03535-3
7. Orme J, Romney JS, Hopkins RO et al (2003) Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med 167:690–694. https://doi.org/10.1164/rccm.200206-542OC
8. González J, Benítez ID, Carmona P et al (2021) Pulmonary function and radiologic features in survivors of COVID-19: A 3-month prospective cohort. Chest 160:187–198. https://doi.org/10.1016/j.chest.2021.02.062
9. Van Aerde N, Meersseman P, Debaveye Y et al (2021) Five-year outcome of respiratory muscle weakness at intensive care unit discharge: secondary analysis of a prospective cohort study. Thorax 76:561–567. https://doi.org/10.1136/thoraxjnl-2020-216720
10. Pandharipande PP, Girard TD, Jackson JC et al (2013) Long-term cognitive impairment after critical illness. N Engl J Med 369:1306–1316. https://doi.org/10.1056/NEJMoa1301372
11. Jackson JC, Pandharipande PP, Girard TD et al (2014) Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med 2:369–379. https://doi.org/10.1016/s2213-2600(14)00051-7
12. Fan E, Brodie D, Slutsky AS (2018) Acute respiratory distress syndrome: advances in diagnosis and treatment. JAMA 319:698–710. https://doi.org/10.1001/jama.2017.21907
13. González-López A, Astudillo A, García-Prieto E et al (2011) Inflammation and matrix remodeling during repair of ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol 301:L500–509. https://doi.org/10.1152/ajplung.00330.2010
14. Dos Santos CC (2008) Advances in mechanisms of repair and remodelling in acute lung injury. Intensive Care Med 34:619–630. https://doi.org/10.1007/s00134-007-0963-x
15. Mack M (2018) Inflammation and fibrosis. Matrix Biol 68–69:106–121. https://doi.org/10.1016/j.matbio.2017.11.010
16. Keim PM, Winston BW (2002) Roles for insulin-like growth factor I and transforming growth factor-beta in fibrotic lung disease. Chest 122:2895–2935
17. Phan THG, Palojiannis P, Nasrallah GK et al (2021) Emerging cellular and molecular determinants of idiopathic pulmonary fibrosis. Cell Mol Life Sci 78:2031–2057. https://doi.org/10.1007/s00134-020-05695-7
18. Madtes DK, Rubenfeld G, Klima LD et al (1998) Elevated transforming growth factor-alpha levels in bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 158:424–430. https://doi.org/10.1164/ajrccm.158.2.9711112
19. Marshall RP, Bellingan G, Webb S et al (2000) Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. Am J Respir Crit Care Med 162:1783–1788. https://doi.org/10.1164/ajrccm.162.5.2001061
20. Chanda D, Otoupalova E, Smith SR et al (2019) Developmental pathways in the pathogenesis of lung fibrosis. Mol Asp Med 65–69. https://doi.org/10.1016/j.mam.2018.08.004
21. Upagupta C, Shimbori C, Alsulmi R, Kolb M (2018) Matrix abnormalities in pulmonary fibrosis. Eur Respir Rev 27:180033. https://doi.org/10.1183/16006177.0033-2018
22. Wygecka M, Jablonska E, Guenther A et al (2008) Current view on alveolar coagulation and fibrinolysis in acute inflammatory and chronic interstitial lung diseases. Thromb Haemost 99:494–501. https://doi.org/10.1160/TH07-11-0666
23. Kalluri R, Weinberg RA (2009) The basics of epithelial-mesenchymal transition. J Clin Invest 119:1420–1428. https://doi.org/10.1172/JCI39104

24. Inui N, Sakai S, Kitagawa M (2021) Molecular pathogenesis of pulmonary fibrosis, with focus on pathways related to TGF-β and the ubiquitin-proteasome pathway. Int J Mol Sci 22:6107. https://doi.org/10.3390/ijms22116107

25. Villar J, Cabrera NE, Valladares F et al (2011) Activation of the Wnt/β-catenin signaling pathway by mechanical ventilation is associated with ventilator-induced pulmonary fibrosis in healthy lungs. PLoS ONE 6:e23914. https://doi.org/10.1371/journal.pone.0023914

26. Cabrera-Navarrete NE, Parotto M, Post M et al (2012) Mechanical stress induces lung fibrosis by epithelial-mesenchymal transition. Crit Care Med 40:510–517. https://doi.org/10.1097/CCM.0b013e31822f9ed7

27. Ordoñez CL, Khoshay R, Wong HH et al (2001) Mild and moderate asthma is associated with airway goblet cell hyperplasia and abnormalities in mucin gene expression. Am J Respir Crit Care Med 163:517–523. https://doi.org/10.1164/ajrccm.163.2.2004039

28. Gohy S, Carlier FM, Fregimilicka C et al (2019) Altered generation of ciliated cells in chronic obstructive pulmonary disease. Sci Rep 9:17963. https://doi.org/10.1038/s41598-019-54292-x

29. Busse WW, Kraft M, Rabe KF et al (2021) Understanding the key issues in the treatment of uncontrolled persistent asthma with type 2 inflammation. Eur Respir J 58:200393. https://doi.org/10.1183/13993003.03939-2020

30. Faner R, Rojas M, Macnee W, Agusti A (2012) Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 186:306–313. https://doi.org/10.1164/rccm.201202-0283PP

31. Samarelli AV, Tonelli R, Heijink I et al (2021) Dissecting the role of mesenchymal stem cells in idiopathic pulmonary fibrosis: cause or solution. Front Pharmacol 12:692551. https://doi.org/10.3389/fphar.2021.692551

32. Blázquez-Prieto J, Huidobro C, López-Alonso I et al (2021) Activation of p21 limits acute lung injury and induces early senescence after acid aspiration and mechanical ventilation. Transl Res 233:104–116. https://doi.org/10.1016/j.trsl.2021.01.008

33. Parimón T, Yao C, Stripp BR et al (2020) Alveolar epithelial type II cells as drivers of lung fibrosis in idiopathic pulmonary fibrosis. Int J Mol Sci 21:E2269. https://doi.org/10.3390/ijms21072269

34. Albaceta GM, Brochard L, Dos Santos CC et al (2021) The central nervous system during lung injury and mechanical ventilation: a narrative review. Br J Anaesth 127:648–659. https://doi.org/10.1016/j.bja.2021.05.038

35. González-López A, López-Alonso I, Pockroti PA et al (2019) Lung purinoceptor activation triggers ventilator-induced brain injury. Crit Care Med 47:e911–e918. https://doi.org/10.1097/CCM.0000000000003977

36. Hossi T, Okuma Y, Matsuda T, Nomura Y (2005) Novel pathway for LPS-induced afferent vagus nerve activation: possible role of nodose ganglion. Auton Neurosci 120:104–107. https://doi.org/10.1016/j.autneu.2004.11.012

37. Steinberg BE, Silverman HA, Robbianti S et al (2016) Vagal-specific neurotransmitters in the sensory vagus nerve. Bioelectrochem Med 37–17

38. Quilez ME, Foster G, Villar J et al (2011) Injurious mechanical ventilation affects neuronal activation in ventilated rats. Crit Care 15:R124. https://doi.org/10.1186/cc10230

39. Quilez ME, Rodríguez-González R, Tunon M et al (2015) Moderate peep after tracheal lipopolysaccharide instillation prevents inflammation and modifies the pattern of brain neuronal activation. Shock 44:601–608. https://doi.org/10.1097/SHK.0000000000000469

40. Gonzalez-Lopez A, Lopez-Alonso I, Aguirre A et al (2013) Mechanical ventilation triggers hippocampal apoptosis by vagal and dopaminergic pathways. Am J Respir Crit Care Med 188:693–702. https://doi.org/10.1164/rccm.201304-0691OC

41. Sahu B, Sandhir R, Naora AS (2018) Two-hit induced acute lung injury impairs cognitive function in mice: a potential model to study cross talk between lung and brain. Brain Behav Immun 73:633–642. https://doi.org/10.1016/j.bbi.2018.07.013

42. Huppenkothen JA, Anderson BJ, Orfila JE et al (2019) Circulating heparan sulfate fragments mediate septic cognitive dysfunction. J Neuroinflamm 16:109. https://doi.org/10.1186/s12974-019-1552-1

43. Garoni M, Papadimitriou K, Perico N et al (2012) Lack of inflammation helps to evaluate functional outcome of critical ill patients with neuromuscular weakness syndromes. Crit Care 16:R239. https://doi.org/10.1186/cc11295

44. Guarnieri B, Bertolini G, Latorrico N (2008) Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. J Neurol Neurosurg Psychiatry 79:838–841. https://doi.org/10.1136/jnnp.2007.142430

45. Weber-Carstens S, Deja M, Koch S et al (2010) Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study. Crit Care 14:R119. https://doi.org/10.1186/cc9074

46. Rincon M, Cid R, Silvestre E et al (2019) Combination of histopathological and electromyographic patterns can help to evaluate functional outcome of critical ill patients with neuromuscular weakness syndromes. Crit Care 23:835–844. https://doi.org/10.1186/s13054-019-2434-7

47. Kerbau F, Brousse M, Collart F et al (2004) Prolonged mechanical ventilation-induced brain injury. Crit Care Med 32:1504–1510. https://doi.org/10.1097/01.ccm.0000135454.03617.7d

48. Martin-Vicente B, Villar J, Jareckis M et al (2012) Acute lung injury and idiopathic pulmonary fibrosis. Crit Care Med 40:510–517. https://doi.org/10.1097/CCM.0b013e31822f9ed7

49. Kalluri R, Weinberg RA (2009) The basics of epithelial-mesenchymal transition. J Clin Invest 119:1420–1428. https://doi.org/10.1172/JCI39104
54. De Jonghe B, Sharshar T, Lefaucheur J-P et al (2002) Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 288:2859–2867. https://doi.org/10.1001/jama.288.22.2859
55. Herridge MS, Chu LM, Matte A et al (2016) The RECOVER program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. Ann J Respir Crit Care Med 194:831–844. https://doi.org/10.1164/rccm.201512-2349OC
56. Puthucheary ZA, Rawal J, McPhail M et al (2013) Acute skeletal muscle wasting in critical illness. JAMA 310:1591–1600. https://doi.org/10.1001/jama.2013.278481
57. Dos Santos C, Hussain SN, Mathur S et al (2016) Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay: a pilot study. Ann J Respir Crit Care Med. https://doi.org/10.1164/rccm.201512-2344OC
58. Li YP, Schwartz RJ, Waddell ID et al (1998) Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-kappaB activation in response to tumor necrosis factor alpha. FASEB J 12:871–880. https://doi.org/10.1096/fasebj.12.10:971
59. Derde S, Hermans G, Derese I et al (2012) Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. Crit Care Med 40:79–89. https://doi.org/10.1097/CCM.0b013e31822d7c18
60. Guttridge DC, Mayo MW, Madrid LV et al (2000) NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. Science 289:2363–2366. https://doi.org/10.1126/science.289.5488.2363
61. Layne MD, Farmer SR (1999) Tumor necrosis factor-alpha and basic fibroblast growth factor differentially inhibit the insulin-like growth factor-I induced expression of myogenin in C2C12 myoblasts. Exp Cell Res 249:177–187. https://doi.org/10.1006/excr.1999.4465
62. Thaloor D, Miller KJ, Gephart J et al (1999) Systemic administration of the NF-kappaB inhibitor curcumin stimulates muscle regeneration after traumatic injury. Am J Physiol 277:C320–329. https://doi.org/10.1152/ajpcell.1999.277.2.C320
63. García-Martínez C, Lloper M, Agell N et al (1995) Ubiquitin gene expression in skeletal muscle is increased during sepsis: involvement of TNF-alpha but not IL-1. Biochem Biophys Res Commun 217:839–844. https://doi.org/10.1006/ bbrc.1995.2848
64. Llopera M, Garcia-Martinez C, Agell N et al (1997) TNF can directly induce the expression of ubiquitin-dependent proteolytic system in rat soleus muscles. Biochem Biophys Res Commun 230:238–241. https://doi.org/10.1006/bbrc.1996.5827
65. Lecker SH, Solomon V, Mitch WE, Goldberg AL (1999) Muscle protein breakdown and the critical role of the ubiquitin-proteasome pathway in normal and disease states. J Nutr 129:2275-2375. https://doi.org/10.1093/jn/ 129.12.2275
66. Li X, Moody MR, Engel D et al (2000) Cardiac-specific overexpression of tumor necrosis factor-alpha causes oxidative stress and contractile dysfunction in mouse diaphragm. Circulation 102:1690–1696. https://doi.org/10.1161/ 01.cir.102.14.1690
67. Hardin BJ, Campbell KS, Smith JD et al (2008) TNF-alpha acts via TNFR1 and muscle-derived oxidants to depress myofibrillar force in murine skeletal muscle. J Appl Physiol (1985) 104:694–699. https://doi.org/10.1152/japplphys iol00898.2007
68. Stasko SA, Hardin BJ, Smith JD et al (2013) TNF signals via neuronal-type nitric oxide synthase and reactive oxygen species to depress specific force of skeletal muscle. J Appl Physiol (1985) 114:1629–1636. https://doi.org/10.1152/ japplphysiol00871.2012
69. Llopera M, Carbó N, López-Soriano J et al (1998) Different cytokines modulate ubiquitin gene expression in rat skeletal muscle. Cancer Lett 133:83–87. https://doi.org/10.1016/0304-3835(98)00216-x
70. Gunston GN, Maish GO, Gilpin T et al (1999) Mechanism of IL-1 induced inhibition of protein synthesis in skeletal muscle. Shock 11:235–241. https://doi.org/10.1097/00024 382‑19990 4000‑00002
71. Osuchowski MF, Welch K, Siddiqui J, Remick DG (2006) Circulating cytokine/inhibitor profiles reshape the understanding of the SIRS/CARS continuum in sepsis and predict mortality. J Immunol 177:1967–1974
72. Jespersen JG, Nedergaard A, Reitelseder S et al (2011) Activated protein synthesis and suppressed protein breakdown signaling in skeletal muscle of critically ill patients. PLoS ONE 6:e18090. https://doi.org/10.1371/journ al.pone.0018090
73. Nara H, Watanabe R (2021) Anti-inflammatory effect of muscle-derived interleukin-6 and its involvement in lipid metabolism. Int J Mol Sci 22:9889. https://doi.org/10.3390/ijms22189889
74. Madaro L, Passafaro M, Sala D et al (2018) Denervation-activated STAT3-IL-6 signalling in fibro-adipogenic progenitors promotes myofibres atrophy and fibrosis. Nat Cell Biol 20:917–927. https://doi.org/10.1038/ s41556‑018‑0151‑y
75. Nelke C, Dziewas R, Minnerup J et al (2019) Skeletal muscle as potential central link between sarcopenia and immune senescence. EBioMedicine 49:381–388. https://doi.org/10.1016/j.ebiom.2019.10.034
76. Langhans C, Weber-Carstens S, Schmidt F et al (2014) Inflammation-induced acute phase response in skeletal muscle and critical illness myopathy. PLoS ONE 9:e92048. https://doi.org/10.1371/journal.pone.0092048
77. Mauro A (1961) Satellite cell of skeletal muscle fibers. J Biophys Biochem Cytol 9:493–495. https://doi.org/10.1083/ jcb.9.2.493
78. Beauchamp JR, Heslop L, Yu DS et al (2000) Expression of CD34 and MyS defines the majority of quiescent adult skeletal muscle satellite cells. J Cell Biol 151:1221–1234. https://doi.org/10.1083/jcb.151.6.1221
79. Hawke TJ, Garry DJ (2001) Myogenic satellite cells: physiology to molecular biology. J Appl Physiol (1985) 91:534–551. https://doi.org/10.1152/jappl.2001.91.5.534
80. Chazaud B, Sonnet C, Lafuste P et al (2003) Satellite cells attract monocytes and use macrophages as a support to escape apoptosis and enhance muscle growth. J Cell Biol 163:1133–1143. https://doi.org/10.1083/jcb.200212046
81. Sonnet C, Lafuste P, Arnold L et al (2006) Human macrophages rescue myoblasts and myotubes from apoptosis through a set of adhesion molecular systems. J Cell Sci 119:2497–2507. https://doi.org/10.1242/jcs.029888
82. Christov C, Christen F, Abou-Khalil R et al (2007) Muscle satellite cells and endothelial cells: close neighbors and privileged partners. Mol Biol Cell 18:1397–1409. https://doi.org/10.1091/mbc.e06-08-0693
83. van Weel V, Deckers MML, Grimbergen JM et al (2004) Vascular endothelial growth factor overexpression in ischemic skeletal muscle enhances myoglobin expression in vivo. Circ Res 95:58–66. https://doi.org/10.1161/01. RES.0000132474.69803.c3
84. Chakravarthy MV, Davis BS, Booth FW (2000) IGF-I restores satellite cell proliferative potential in immobilized old skeletal muscle. J Appl Physiol (1985) 89:825–833. https://doi.org/10.1152/jappl.2000.89.4.14365
85. Novak KR, Nardelli P, Cope TC et al (2009) Inactivation of sodium channels underlies reversible neuropathy during critical illness in rats. J Clin Invest 119:1150–1158. https://doi.org/10.1172/jci36570
86. Schwarz J, Planck J, Biegel J, Straube A (1997) Single-fiber electromyography, nerve conduction studies, and conventional electromyography in patients with critical-illness polyneuropathy: evidence for a lesion of terminal motor muscle. Muscle Nerve 20:696–701. https://doi.org/10.1002/(SICI)1097-0261(199706)20:6<696::AID-MUS696>3.0.CO;2-3
87. Bhattacharyya J, Thompson KD, Sayeed MM (1993) Skeletal muscle Ca2+
flux and catabolic response during sepsis. Am J Physiol 265:R487–493. https://doi.org/10.1152/ajpregu.1993.265.3.R487
88. Z’Graggen WJ, Lin CSY, Howard RS et al (2006) Nerve excitability changes in critical illness polyneuropathy. Brain 129:2461–2470. https://doi.org/10.1093/brain/awl191
89. Rich MM, Printer MJ (2003) Crucial role of sodium channel fast inactivation in muscle fibre inexcitability in a rat model of critical illness myopathy. J Physiol 547:555–566. https://doi.org/10.1113/jphysiol.2002.035188
90. Fredriksson K, Tjäder J, Keller P et al (2008) Dysregulation of mitochondrial dynamics and the muscle transcriptome in ICU patients suffering from sepsis induced multiple organ failure. PLoS ONE 3:e3686. https://doi.org/10.1371/journal.pone.0003686
91. Masiero E, Agatea L, Mammucari C et al (2009) Autophagy is required to maintain muscle mass. Cell Metab 10:507–515. https://doi.org/10.1016/j.cmet.2009.10.008
92. Mart MF, Pun BT, Pandharipande P et al (2021) ICU survivorship—the relationship of delirium, sedation, dementia, and organ dysfunction in ICU patients suffering from sepsis induced multiple organ failure. PLoS ONE 3:e3686. https://doi.org/10.1371/journal.pone.0003686
93. Mayr M, Hu Y, Hainaut H, Xu Q (2002) Mechanical stress-induced DNA damage and rac-p38MAPK signal pathways mediate p53-dependent apoptosis in vascular smooth muscle cells. FASEB J 16:1423–1425. https://doi.org/10.1096/fj.02-0042fe
94. López-Alonso I, Blázquez-Prieto J, Amado-Rodríguez L et al (2018) Preventing loss of mechanosensation by the nuclear membranes of alveolar cells reduces lung injury in mice during mechanical ventilation. Sci Transl Med 10:aam7598. https://doi.org/10.1126/scitranslmed.aam7598
95. Lahiri S, Regis GC, Koronyo Y et al (2019) Acute neuropsychological consequences of short-term mechanical ventilation in wild-type and Alzheimer’s disease mice. Crit Care 23:63. https://doi.org/10.1186/s13054-019-2356-2
96. Freund A, Orjalo AV, Desprez P-Y, Campisi J (2010) Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med 16:238–246. https://doi.org/10.1016/j.molmed.2010.03.003
97. Pakos-Zebrucka K, Koryga I, Mnich K et al (2016) The integrated stress response. EMBO Rep 17:1374–1395. https://doi.org/10.15252/embr.201642195
98. Dolinay T, Himes BE, Shumyatcher M et al (2017) Integrated stress response mediates epithelial injury in mechanical ventilation. Am J Respir Cell Mol Biol 57:193–203. https://doi.org/10.1165/rcmb.2016-0404OC
99. Lopez AD, Avasarala S, Grewal S et al (2009) Differential role of the Fas/Fas ligand apoptotic pathway in inflammation and lung fibrosis associated with reovirus 1/L-induced bronchiolitis obliterans organizing pneumonia and acute respiratory distress syndrome. J Immunol 183:8244–8257. https://doi.org/10.4049/jimmunol.0901958
100. Llano-Diez M, Fury W, Okamoto H et al (2019) RNA-sequencing reveals altered skeletal muscle contraction, E3 ligases, autophagy, apoptosis, and chaperone expression in patients with critical illness myopathy. Skelet Muscle 9:9. https://doi.org/10.1186/s12391-018-0856-2
101. Imai Y, Parodo J, Kajikawa O et al (2003) Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 289:2104–2112
102. Lopez AD, Avaznara S, Grewal S et al (2009) Differential role of the Fas/Fas ligand apoptotic pathway in inflammation and lung fibrosis associated with reovirus 1/L-induced bronchiolitis obliterans organizing pneumonia and acute respiratory distress syndrome. J Immunol 183:8244–8257. https://doi.org/10.4049/jimmunol.0901958
103. Chillde BC, Baker DJ, Kirkland JL et al (2014) Senescence and apoptosis: dueling or complementary cell fates? EMBO Rep 15:1139–1153. https://doi.org/10.15252/embr.201442195
104. Justice JN, Nambari AM, Tchkonia T et al (2019) Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study. EBioMedicine. https://doi.org/10.1016/j.ebiom.2018.12.052
112. Kosyakovsky LB, Angriman F, Katz E et al (2021) Association between sepsis survivorship and long-term cardiovascular outcomes in adults: a systematic review and meta-analysis. Intensive Care Med 47:931–942. https://doi.org/10.1007/s00134-021-06479-y

113. Mankowski RT, Yende S, Angus DC (2019) Long-term impact of sepsis on cardiovascular health. Intensive Care Med 45:78–81. https://doi.org/10.1007/s00134-018-5173-1

114. Landesberg G, Levin PO, Gilion D et al (2015) Myocardial dysfunction in severe sepsis and septic shock: no correlation with inflammatory cytokines in real-life clinical setting. Chest 148:93–102. https://doi.org/10.1378/chest.14-2259

115. Merdji H, Kassem M, Chomel L et al (2021) Septic shock as a trigger of arterial stress-induced premature senescence: a new pathway involved in the post sepsis long-term cardiovascular complications. Vascul Pharmacol. https://doi.org/10.1016/j.vph.2021.106922

116. Haines RW, Powell-Tuck J, Leonard H et al (2021) Long-term kidney function of patients discharged from hospital after an intensive care admission: observational cohort study. Sci Rep 11:9928. https://doi.org/10.1038/s41598-021-89454-3

117. Basile DP, Bonventre JV, Mehta R et al (2016) Progression after AKI: understanding maladaptive repair processes to predict and identify therapeutic treatments. J Am Soc Nephrol 27:687–697. https://doi.org/10.1681/ASN.2015030309

118. Yang L, Besschetnova TY, Brooks CR et al (2010) Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. Nat Med 16:535–543. https://doi.org/10.1038/nm.2144 (1p following 143)

119. Bomans K, Schenz J, Tamulyte S et al (2018) Paternal sepsis induces alterations of the sperm methylome and dampens offspring immune responses—an animal study. Clin Epigenetics 10:89. https://doi.org/10.1186/s13148-018-0522-z

120. Zhang Z, Zhao Y, Zhang Y et al (2020) Paternal systemic inflammation induces offspring programming of growth and liver regeneration in association with IGF2 upregulation. Mol Cell Endocrinol 518:111001. https://doi.org/10.1016/j.mce.2020.111001

121. Nagy C, Turecki G (2015) Transgenerational epigenetic inheritance: an open discussion. Epigenomics 7:781–790. https://doi.org/10.2217/epi.15.46

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