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Abstract

Systemic inflammation is known to target tubular epithelial cells (TECs), leading to acute kidney injury. Tubular cells have been implicated in the response to inflammatory mediators in ischaemic and septic renal damage. Moreover, loss of tubular cells by apoptosis or epithelial-to-mesenchymal transition may ingenerate conditions that lead to progression towards chronic kidney disease. On the other hand, TECs may actively contribute to the production of inflammatory mediators that may propagate the injury locally or in distant organs. In the present review, we discuss the tubular cell response and its contribution to systemic inflammation.

INTRODUCTION

An excessive inflammatory response may induce tissue injury through the direct detrimental activity of circulating cytokines and chemokines. An increasing body of evidence suggests that kidney tubular epithelial cells (TECs) operate as professional immune cells, modulating both innate and adaptive immune responses. Indeed, lipopolysaccharides (LPS) and other pathogen-associated molecular patterns (PAMPs) are known to directly interact with toll-like receptor (TLR)-2 and TLR-4 located on TECs, and to induce the release of several cytokines, including IL-6, *IL-10, IL-18, IP-10, KC, MCP-1* and tumour necrosis factor-α (TNF-α), via the TLR adapter protein MyD88 (Myeloid Differentiation Factor 88) [1–3]. This pro-inflammatory effect on TECs ultimately leads to leucocyte extravasation and infiltration, with perpetuation of tissue damage. Moreover, activated TECs are known to interact directly with neutrophils, monocytes and T cells, through the expression of cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and P-selectin [2]. TECs are antigen-presenting cells and express class I and II MHC, which are essential in mediating the interaction of TECs with $CD4^+$ T-helper cells in immune-mediated renal disease, as well as in kidney graft rejection. It has also been shown that class II MHC and TLRs co-localize on the surface of TECs in lipid rafts, and synergize in the activation of intracellular pathways [4]. In addition, TECs express co-stimulatory molecules, such as B7-1 and CD40, on their surface, which may trigger release of inflammatory mediators during immune-mediated renal diseases [5].

We herein review the effects of systemic inflammation on tubular cells in the setting of acute kidney injury (AKI) and progression toward chronic kidney disease (CKD), and TEC contribution to distant organ damage associated with systemic inflammation.

INFLAMMATION AND ISCHAEMIC AKI

AKI is a worldwide health problem, usually associated with multiple organ failure and characterized by high mortality rates and progression towards end-stage renal disease [6]. The inflammatory response is an important contributor to tissue damage associated with AKI, leading to derangement of the microvasculature and functional alterations of tubular cells. Plasma levels of inflammatory cytokines are significantly higher in patients with AKI than in healthy subjects and are associated with an increased risk of mortality [7]. Moreover, Jaber *et al.* [8] demonstrated that the TNF-α high-producer genotype (-308 A-allele carrier) is associated with a higher risk of death, whereas the IL-10 intermediate/high-producer genotype (-1082 G-allele carrier) is associated with a lower risk of death.

The local production and release of inflammatory mediators may contribute to the reduction of blood flow in the outer medulla, with adverse consequences on tubular function and viability [9]. Furthermore, the innate and adaptive immune responses strongly contribute to the pathogenic mechanisms of ischaemic-,

toxic- and sepsis-associated AKI. The innate immune system is accountable for the early response to infection or ischaemic injury. TLRs on TECs are up-regulated in response to endogenous ligands and play a critical role in detecting exogenous microbial products and developing antigen-dependent adaptive immunity [4]. TLRs can mediate a strong pro-inflammatory response, which includes activation and maturation of dendritic cells, which in turn are known to activate antigen-specific naïve T cells, hence triggering the adaptive immune response [1]. In experimental models of AKI in mice, the absence of TLR2 and TLR4 was associated with a potent anti-inflammatory effect and functional protection [3]. Wu *et al.* [10] found that TLR4 expression by TECs is up-regulated by ischaemia–reperfusion injury *in vivo* and by hypoxic conditions *in vitro*. Moreover, following renal ischaemia–reperfusion injury, endothelial cells contribute to organ dysfunction by up-regulation of integrins, selectins and members of the immunoglobulin superfamily, including ICAM-1 and vascular cell adhesion molecule. An enhanced leucocyte–endothelial interaction can result in cell-to-cell adhesion which leads to a decreased blood flow, causing deterioration of renal damage [11]. The up-regulation of ICAM-1 is associated with an increased release of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β. Later phases of AKI are characterized by interstitial infiltration of macrophages and T lymphocytes that predominate on neutrophils. In addition to inflammatory cytokines, reactive oxygen species (ROS) are generated during reperfusion and play a major role in TEC injury.

TECs not only contribute to the inflammatory reaction through generation of chemotactic cytokines such as TNF-α, MCP-1, IL-8, IL-6, IL-1β and TGF-β, MCP-1, IL-8, RANTES and ENA-78, but they also activate T lymphocytes [12]. The co-stimulatory molecule CD40, located on the surface of proximal TECs, is activated by the binding of its specific ligand CD154. The CD40–CD154 interaction induces MCP-1, RANTES and IL-8 production, along with TRAF6 recruitment and MAPK activation [12].

A prominent role in the cross-talk between the inflammatory response and tubular injury can be ascribed to infiltrating leucocytes. Indeed, neutrophil-depleted animals are protected from ischaemic AKI [13]. T cells also participate in the mechanisms of renal ischaemia–reperfusion injury. Li *et al.* [14] found that IFN-γ–producing $CD4^+$ T cells and NK cells are necessary to induce neutrophil infiltration in the kidney. Moreover, depletion of NK cells led to attenuation of ischaemia–reperfusion injury [14].

Several immunomodulatory factors are involved in the control of innate immunity during AKI, for example IL-15 acts as an autocrine epithelial survival factor by means of its receptor IL-15Rγ (CD132). IL-15 preserves E-cadherin expression, inhibiting both apoptosis and the epithelial-to-mesenchymal transition (EMT). Conversely, during allograft rejection, the increased intra-graft IL-15 expression favours tubular destruction, facilitating intra-epithelial recruitment of CD8+ T cells expressing the E-cadherin ligand CD103 [15].

The inflammatory response is known to be inhibited by transforming growth factor-β (TGF-β), which is an anti-apoptotic cytokine. However, TGF-β may also induce chronic interstitial fibrosis and activate the EMT, and recent data have demonstrated a direct role of TGF-β as a mediator of AKI [16].

Jung *et al.* [17] demonstrated that infusion of macrophages over-expressing IL-10 in a rat model of ischaemia–reperfusion led to increased tubular expression of NGAL, megalin and regenerative markers, as well as causing improved kidney function; these beneficial effects were abrogated both by anti-NGAL antibodies and iron chelating molecules.

Macrophage-stimulating protein (MSP) is a plasminogen-related growth factor produced by the liver and TECs. MSP promotes macrophage chemotaxis, phagocytosis and cytokine production. In a toxic model of AKI, MSP stimulated proliferation of TECs and significantly inhibited apoptosis by the down-regulation of Fas and the over-expression of the anti-apoptotic mitochondrial protein Bcl-xL [18].

SEPSIS-ASSOCIATED AKI

The role of systemic inflammation is particularly relevant in the context of sepsis-associated AKI. The mechanisms of renal damage appear to be complex and multi-factorial, and include intra-renal haemodynamic changes, endothelial dysfunction, infiltration of inflammatory cells, intra-glomerular thrombosis and obstruction of tubular lumen due to the deposition of necrotic cells and debris [19]. In the course of sepsis, the dogma of kidney hypoperfusion caused by hypovolemia-related distributive shock has been challenged by recent studies showing that cardiac output is considerably increased, and kidney damage occurs in the presence of a normal or even increased blood flow [9]. In addition, a growing body of evidence suggests that the sepsis-induced immune response involves the activation of both pro- and anti-inflammatory mechanisms that are responsible for immunoparalysis and multiple organ failure [19]. On this basis, a new 'toxic-immunologic' theory for the pathogenesis of sepsis-associated AKI indicates the role of circulating detrimental mediators that are able to induce apoptosis and/or necrosis of tubular cells and derangement of microcirculation [20]. After initial host–microbial interactions, a widespread activation of the innate immune system has been described, which coordinates a defensive response involving both humoral and cellular components, finally leading to the secretion of various cytokines.

Different PAMPs, including LPS and other microbial products such as lipoteichoic acid and porins, have been demonstrated to directly interact with resident kidney cells. The detrimental effects of LPS are mainly due to its influence on tubular cells after binding to TLR-4 [4]. Moreover, LPS reduces the expression of the endocytic receptors megalin and cubilin in the apical compartment of proximal TECs, which interferes with the processes of protein re-absorption, contributing to the typical low molecular weight proteinuria of septic patients [21]. An additional function of LPS is the synergism with inflammatory cytokines, leading to induction of TNF-mediated tubular cell apoptosis [22]. TNF-α and Fas-ligand can bind directly to tubular cell receptors, inducing activation of caspase-8 and triggering the death receptor pathway of apoptosis [19]. *In vitro* studies have confirmed that the plasma of septic patients is able to induce functional alterations and apoptosis of both glomerular and TECs [23]. All these findings support the hypothesis that acute apoptosis plays a pivotal role in the pathogenic mechanisms of AKI, multiple organ failure and immunoparalysis during sepsis. This may account for the paucity of histological alterations detected in kidneys of septic patients, in particular the lack of acute tubular necrosis. This was recently confirmed by Lerolle *et al.* [24], who showed the presence of typical signs of apoptosis, such as DNA fragmentation and caspase-3 staining, in renal tubular cells of patients who had died from sepsis. More recent studies have suggested a putative role of histone release from necrotic cells in the mechanisms of sepsis-associated tissue injury. Xu *et al.* [25] demonstrated that post-necrotic histone release in septic baboons is a major determinant of neutrophil margination, endothelium vacuolization, intra-alveolar haemorrhage and macro- and microvascular thrombosis. Histone release also induces tubular injury through direct activation of TLR2 and TLR4 [3]. In addition, histone cleavage by activated protein C reduces sepsis-related mortality [25].

An additional pathogenic mechanism of sepsis-associated AKI is the alteration of mitochondrial function and activity. Indeed, during sepsis, tissues undergo a reduction of cellular respiration similar to that observed under hypoxic conditions and several mitochondrial alterations have been described at the tubular level. Tran *et al.* also showed that the presence of PPARγ coactivator-1α (PGC-1α), a major regulator of mitochondrial biogenesis and metabolism, is decreased in tubular cells in septic AKI, with TNF-α being the main determinant of reduced PGC-1α expression in tubular cells. Both global and tubule-specific PGC-1α-knockout mice are more sensitive to LPS-induced tubular injury [26].

INFLAMMATORY MECHANISMS AND AKI IN KIDNEY TRANSPLANTATION

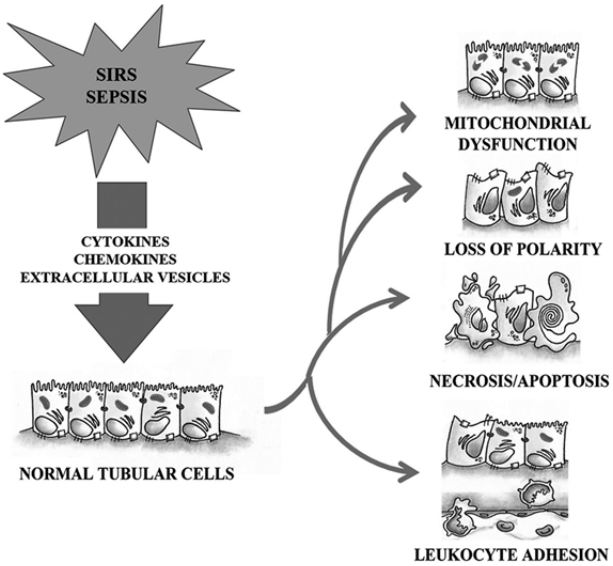
Systemic inflammation triggered by ischaemic or immune-mediated causes may play a relevant role in tubular injury in kidney grafts. Ischaemia–reperfusion injury is the primary cause of delayed graft function (DGF) [27]. The mechanisms of DGF are similar to those described for ischaemia–reperfusion injury in native kidneys; however, deterioration of hypoxia-associated tissue damage can be caused by nephrotoxic drugs, in particular calcineurin inhibitors [27]. Systemic inflammation and circulating cytokines play a key role in leucocyte infiltration into ischaemic kidney grafts. Famulski *et al.* [28] showed that in kidney transplant recipients with rejection-unrelated AKI, the transcripts associated with an injury-repair response

correlated with a history of DGF, a decrease of GFR at the time of biopsy and interstitial inflammation. Inflammatory mediators play a role, not only in ischaemia–reperfusion injury, but also in the mechanisms of rejection. Indeed, several studies have demonstrated that cytokine gene polymorphisms may influence the outcome of kidney transplantation. A TNF-α -308AA-genotype has been shown to be a pre-disposing factor for acute rejection episodes [29]. Tubular cells are targets of T-cell-mediated rejection (TCMR), characterized by so-called tubulitis, mediated by infiltrating T lymphocytes able to secrete paracrine factors such as Fas-ligand, perforins and granzyme B that trigger TEC apoptosis [30]. More recently, it has been shown that the inflammatory response during TCMR induces an injury-repair response similar to that observed after ischaemia–reperfusion injury [31]. In particular, the inflammatory environment leads to down-regulation of solute carriers in tubular cells, which play a critical role in the maintenance of polarity, adsorption, metabolism and clearance of tubular cells. The loss of solute carriers during TCMR results in de-differentiation of tubular cells, and activation of the epithelial-to-mesenchymal transition responsible for the progression toward tubulo-interstitial fibrosis and loss of graft function [31].

MECHANISMS INVOLVED IN TUBULAR CELL DYSFUNCTION AND PROGRESSION TOWARD CKD

Several mechanisms contributing to injury of tubular cells have been described during ischaemic-, toxic- and septic-AKI (Figure 1). The first alterations at the cellular level are related to loss of polarity and the inability of tubular cells to maintain distinct fluid-filled compartments with precise electrolyte concentrations [7]. The loss of cell polarity is due to the altered expression of proteins that are usually located at the apical or basal part of tubular cells and to the down-regulation of tight junction proteins, in particular ZO-1 and occluding [32]. If the injury persists, tubular cells undergo necrosis, apoptosis or necroptosis, a form of regulated necrotic cell death pathway controlled by receptor-interacting protein kinase (RIPK)1 and RIPK3 [33]. As previously stated, apoptosis sensitivity of tubular cells is mediated by membrane expression and activation of TNF-R and Fas. Intracellular survival and death signals in the presence of inflammatory mediators can also be orchestrated by the mitochondrial apoptosis pathway, in particular by the BCL2 protein family, to which Bax and Bak belong. These proteins promote tubular apoptosis by fragmentation of outer mitochondrial membrane and subsequent caspase activation, whereas Bcl-2 and Bcl-XL antagonize membrane alteration [34]. Many other molecules regulate this complex balance of pro- and anti-apoptotic factors, which may therefore be considered as a therapeutic target. For example glycogen synthase kinase 3-β (GSK3β) promotes pro-apoptotic signals, and its pharmacological inhibition improves AKI in different *in vivo* models [34].

FIGURE 1



Mechanisms of tubular cell injury in the presence of systemic inflammation. SIRS, systemic inflammatory response syndrome.

RIPKs represent a second-line defence mechanism of the host, against viruses that express caspase-8 inhibitors. During AKI, the combination of several humoral signals (such as IFN-γ and TNF-α) may invert the RIPK/caspase-8 ratio, promoting necroptosis [33]. Recent data have also confirmed the relevance of the RIPK pathway in kidney transplantation. Lau *et al.* [35] demonstrated that RIPK3-mediated necroptosis promotes inflammation and reduces survival of kidney allografts.

Autophagy is a cellular mechanism of 'self-eating' whereby cytoplasm components are sequestered into autophagic vesicles or vacuoles (autophagosomes) and delivered to lysosomes, and this process is regulated by a large family of genes (autophagy-related genes, Atgs). The role of autophagy in AKI is far from being fully elucidated. Jiang *et al.* [36] demonstrated that autophagy inhibition by chloroquine administration, or by Atg-7 knock-out, exacerbates both cisplatin- and ischaemic-related AKI in mice. In addition, activation of autophagy by the mTOR inhibitor rapamycin has been shown to be renoprotective.

Another mechanism of tubular cell dysfunction associated with de-differentiation is the epithelial-to-mesenchymal transition, a process caused by aberrant repair leading to tissue fibrosis, for the overproduction of pro-fibrotic agents such as TGF-β, CTGF and type I collagen. The Bonventre group [37] demonstrated that post-injury fibrosis is promoted by the arrest of tubular cells in the G2/M phase cell cycle. Indeed, the arrest of tubular cells in this phase leads to activation of c-jun NH(2)-terminal kinase (JNK) signalling that in turn up-regulates the production of pro-fibrotic cytokines, causing the switch from a tubular phenotype to fibroblast-like gene expression [37].

There is growing interest in defining the role of uraemic toxins in the mechanisms of CKD progression. Middle molecules including pro-inflammatory peptides and cytokines and protein-bound uraemic toxins, such as p-cresyl sulphate and indoxyl sulphate, may play a role in microvascular rarefaction, tubulo-interstitial fibrosis and chronic hypoxia, favouring the progression toward CKD [38]. P-cresyl sulphate and indoxyl sulphate derive from bacterial intestinal metabolism and tend to accumulate in the course of CKD [38]. The organic anion transporters OAT1 and OAT3 mediate the transport of indoxyl sulphate to proximal tubules. In experimental models of CKD, OAT1 and OAT3 expression are reduced, leading to indoxyl sulphate accumulation in renal tubules [39].

Indoxyl sulphate appears to cause renal tubular damage by means of oxidative stress, and promotes tubulo-interstitial fibrosis and glomerular sclerosis. In addition, indoxyl sulphate promotes activation of NF-kB p65 through ROS, followed by expression of p53 and cellular senescence [40]. This effect may also be mediated by the decreased expression of Klotho, an anti-aging gene, the deficiency of which promotes tubular senescence and the increased expression of fibrosis-related genes, inflammatory mediators and chemokines [40].

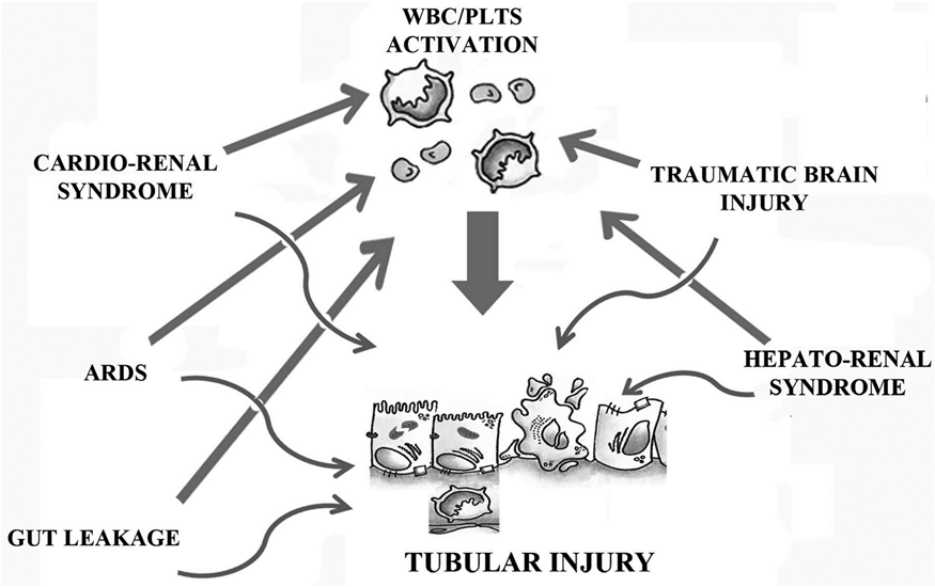
Another potential mechanism of CKD progression is related to the phenotype of resident mononuclear cells. Thus, factors such as IL-1 receptor-associated kinase-M (IRAK-M), a macrophage-specific inhibitor of TLRs and IL1-R, have been shown to influence CKD. IRAK-M deficiency had no effect at Day 1 after ischaemic AKI, but resulted in severe pathology within 5 weeks after injury [41].

The ubiquitin ligase Murine Double Minute-2 (MDM-2) is known to promote cancer cell survival and growth by degrading the cell cycle regulator p53. *In vivo,* the inhibition of MDM-2 impairs tubular cell regeneration after ischaemia–reperfusion injury. Conversely, MDM2 blockade prevents tubular necrosis in the early injury phases of AKI by down-regulation of pro-inflammatory NFκB-dependent cytokine expression [42].

INFLAMMATION, TUBULAR INJURY AND ORGAN CROSS-TALK

AKI is rarely an isolated event, but often occurs in a clinical scenario of multiple organ failure. Several diseases affecting distant organs may lead to an excessive inflammatory response with consequent tubular injury (Figure 2).

FIGURE 2



Main pathological conditions in distant organs leading to systemic inflammation, tubular epithelial cell injury and AKI. ARDS, acute respiratory distress syndrome; WBC, white blood cells; PLTS, platelets.

The cross-talk between the lungs and kidneys has been intensively studied in critically ill patients. Both organs are main targets during severe sepsis and septic shock, and the development of pneumonia is often associated with alterations in renal function due to a systemic inflammatory reaction. Furthermore, ventilator-associated alveolar stretch and biotrauma are well recognized causes of acute lung injury. Studies performed *in vivo* and *in vitro* using plasma derived from patients treated with different ventilatory strategies showed that both type I and II pneumocytes can produce IL-1β, IL-6, IL-8 and TNF-α after biotrauma and that the release of these cytokines promotes tubular cell apoptosis and AKI [43].

Cardio-renal syndrome (CRS) is defined as a primary disorder of the heart or kidneys whereby acute or chronic dysfunction originating from one organ may induce acute or chronic dysfunction of the other [44]. Type 1 CRS reflects an acute deterioration of cardiac function, whereas type 2 CRS is associated with chronic abnormalities of cardiac function able to induce AKI and progressive CKD.

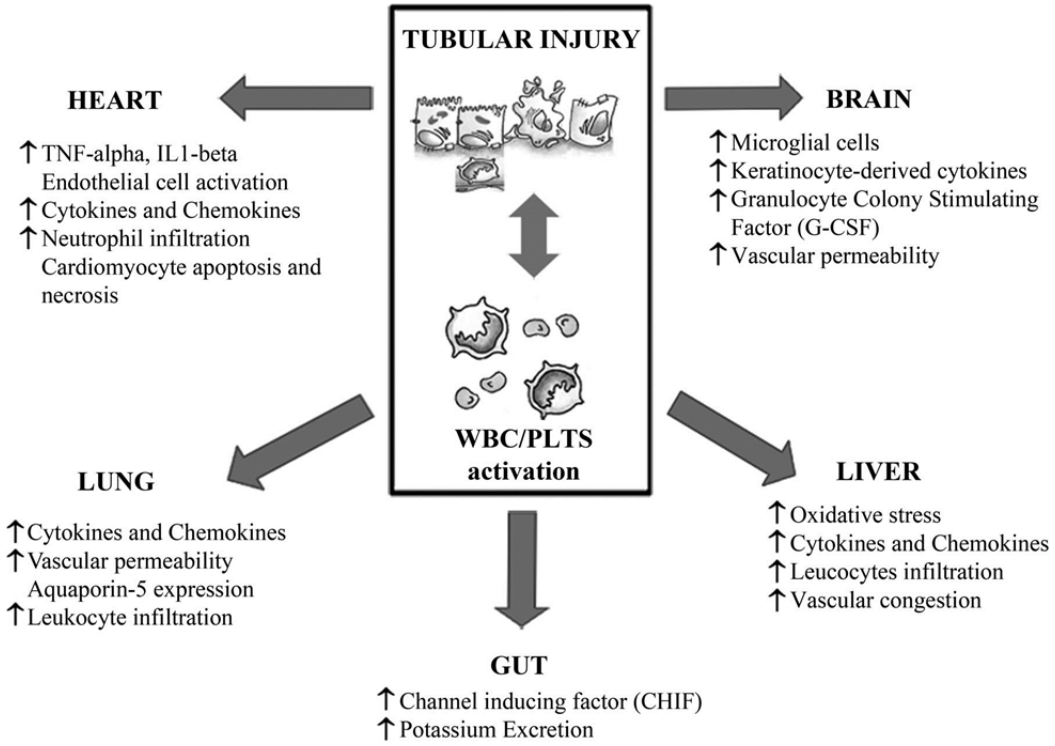
The pathophysiologic basis of type 1 and 2 CRS may be ascribed to the activation of sympathetic and parasympathetic innervations, the renin–angiotensin–aldosterone system, oxidative stress and release of free oxygen radicals, thus favouring apoptosis and fibrosis, with progression of both renal and cardiac dysfunction [44]. In type 1 and 2 CRS, tubular cells, as well as cardiomyocytes, contribute to the release of a broad spectrum of inflammatory cytokines such as TNF-α and IFN-γ, the levels of which are closely related to major clinical outcomes, including mortality.

The interaction between liver disease, systemic inflammation and renal damage is also well known [45]. Hepato-renal syndrome is a functional form of AKI that frequently occurs in patients with advanced cirrhosis and severe impairment of systemic circulatory function. The pathogenesis of this syndrome is primarily related to a state of hyperdynamic circulation with alteration of splanchnic blood flow, due to the imbalance between endothelin-1 and NO production and the increase of systemic ammonium. However, a role is being increasingly attributed to systemic inflammation, and therapeutic approaches of TNF-α down-regulation with pentoxifylline, or antagonism with the monoclonal antibody etanercept have been proposed [45].

Ischaemic, toxic or traumatic brain injury is also associated with systemic inflammation and renal dysfunction. This is of particular relevance during the 'cytokine storm' observed after brain death. In the case of organ donation, the increased amount of circulating inflammatory mediators following brain dysfunction may lead to tubular cell apoptosis/necrosis with an increased risk of DGF [46].

On the other hand, several studies have described histological and transcriptional alterations in distant organs following AKI, particularly due to ischaemia–reperfusion injury (Figure 3). Indeed, considering the improvements in renal support therapies, the majority of the mortality risks for AKI patients comes from distant organ dysfunction [6]. Identification of the mechanisms by which AKI affects distant organ function is critical to the development of selected therapies able to prevent, or at least to limit, AKI-associated co-morbidities and mortality. Inflammatory cytokines have been identified as the potential mediators of these remote effects of AKI [47].

FIGURE 3



Main distant organ dysfunctions associated with the systemic inflammatory reaction following AKI.

In type 3 CRS, AKI leads to acute cardiac dysfunction. The pathogenic mechanisms of cardiomyocyte injury after ischaemic AKI can be ascribed to apoptosis associated with increased plasma levels of TNF-α. Indeed, TNF-α blockade has been shown to limit cardiac apoptosis [44].

In a mouse model of ischaemic AKI-induced lung dysfunction, Rabb *et al.* [48] showed the down-regulation of aquaporins and sodium channels in pneumocytes. In addition, the inflammatory response that follows AKI leads to the activation of several apoptosis-related genes. The authors showed that pulmonary apoptosis is an important pathogenic mechanism and that AKI is responsible for the triggering of pulmonary pro-apoptotic pathways.

AKI has also been shown to induce inflammation and functional changes in the brain. Indeed, animals subjected to experimental AKI showed increased neuronal pyknosis and microgliosis in the brain, in association with increased levels of pro-inflammatory chemokines [49].

The inflammatory response associated with AKI may also lead to the alteration of intestinal permeability, with a consequent increase in translocation of bacterial products [50].

Naito *et al.* demonstrated that AKI sensitizes the kidney to LPS-driven production of cytokines and chemokines. This hyper-responsiveness to LPS seems to be mediated by the increase of histone methylation and consequent recruitment of RNA polymerase II to the TNF-α and MCP-1 genes [22].

CONCLUSIONS

In conclusion, TECs are not only targets of inflammatory mediators, but they may also contribute to their production. Inflammatory mediators derived from TECs may, on one hand, contribute to the development and progression of renal injury and, on the other hand, may mediate distant organ dysfunction. The recognition of an active contribution of inflammatory mediators produced systemically or locally should influence therapeutic approaches aimed at counteracting their production or action. Therefore, inflammation represents an important target for pathogenic interventions in AKI and CKD progression.

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