Chapter 8
Sepsis-Induced AKI

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Introduction

Sepsis is thought to be the primary etiology of acute kidney injury (AKI) in 40–50% of cases, making sepsis the most common cause of AKI in the critically ill [1]. Importantly, the development of AKI in the setting of sepsis increases the risk of death in hospital six to eightfold [1, 2], and among survivors, the risk of developing chronic kidney disease is also increased [3]. Despite this, the mechanisms by which sepsis causes AKI are not well understood, and hence current therapy remains reactive rather than preventive, and rather nonspecific. Given that the leading clinical conditions associated with AKI, namely, sepsis, major surgery, heart failure, and hypovolemia [1], are all associated with hypoperfusion, it is tempting to attribute all AKI to ischemia. However, an increasing body of evidence suggests that at least in a proportion of patients, AKI can occur in the absence of overt signs of hypoperfusion. Langenberg et al. showed, for example, that AKI developed in septic animals despite normal or increased renal blood flow [4]. In a human study, Prowle et al. were able to demonstrate that decreased renal blood flow (RBF) was not a universal finding even in patients with well-established sepsis-induced AKI [5]. Furthermore,

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in a large-scale study, including more than 1800 patients with community-acquired pneumonia, Murugan et al. found that a fifth to a quarter of patients with non-severe pneumonia, who were never admitted to an ICU, and who never displayed overt signs of shock or hypoperfusion, still developed AKI [6]. Complementary to the insights from clinical and in vivo studies, in vitro experiments where hemodynamics are no longer relevant, have shown that incubation of human renal tubular epithelial cells with plasma from septic patients induces damage of tubular epithelial cells evidenced by the increased release of tubular enzymes, elevated permeability, and the decreased expression of key molecules for tubular functional integrity [7]. Taken together these data provide evidence that, at least in some patients, renal injury cannot be explained solely on the basis of the classic paradigm of hypoperfusion and that other mechanisms must come into play.

One of the limitations in advancing the understanding of sepsis-induced AKI is the lack of pathologic specimens available, given that the risk of performing biopsies in this patient population outweighs any potential benefit. Recent studies in septic animals and postmortem observations in septic humans have provided evidence of what sepsis-induced AKI actually looks like. Despite representing the latest stages of the disease, these kidneys were characterized by a strikingly bland histology with focal areas of tubular injury, which was also entirely discordant with the profound functional impairment seen pre-mortem. In addition, and contrary to prior understanding, necrosis and apoptosis were largely absent [8, 9], which not only argues in favor of the notion that sepsis-induced AKI is not equivalent to acute tubular necrosis (ATN), but supports the hypothesis that at least in the early stages, this phenotype may represent a concerted, organized, common underlying adaptive mechanism [9]. A consistent observation in these studies, regardless of species, disease stage, severity, or organ examined, appears to be the presence of three main alterations: inflammation [10, 11], diffuse microcirculatory flow abnormalities [12], and cellular bioenergetic adaptive responses to injury [9, 13]. The study and understanding of these three domains may provide a roadmap to unravel the mechanisms by which sepsis causes AKI and perhaps organ injury in general and may facilitate the development of more targeted therapies. In this chapter, we will first consider the current classification system for AKI and then briefly review the epidemiology; then we will review the roles various mechanisms may play in the genesis of sepsis-induced AKI and discuss potential therapeutic implications.

Definition of AKI in the Clinical Setting

The definition of AKI has undergone important transformations in recent years. The definition of AKI has been traditionally based on the assessment of renal function, and in particular, on the assessment of changes in glomerular filtration rate (GFR). Although practical at the bedside, this approach is limited by the fact that functional changes not necessarily reflect structural alterations [3]. This is particularly true in

sepsis-induced AKI, where a dramatic alteration in renal function is associated with very bland histology [8, 9]. An additional limitation is the assessment of GFR through the quantification of creatinine. Although creatinine levels correlate well with GFR in steady-state conditions, AKI usually occurs in the setting of changing physiologic or pathologic conditions. Finally, the assessment of renal dysfunction based on glomerular function does not take into account the presence of tubular dysfunction, which has been increasingly recognized as an important pathophysiologic event, and to be at least as important as the alterations in GFR. Despite these limitations, the standardization of two measures of glomerular function has provided the scientific community with a tool, in a common language, to assess the occurrence of AKI. These measures are serum creatinine and urine output. Today, the evaluation of the presence and degree of severity of AKI can be standardized with tools like the KDIGO criteria [14].

The Epidemiology of Sepsis-Induced AKI

Sepsis is the leading cause of acute kidney injury (AKI) in acutely ill patients. Acute kidney injury occurs in as much as 40–50% of septic critically ill patients, which increases the risk of death six- to eightfold [1, 2, 15, 16], and also the risk of advancing to renal fibrosis and chronic kidney disease [3]. Importantly, a large proportion of patients who are usually considered to be less severely compromised and thus at lower risk, still develop AKI. Murugan et al. showed in a large cohort of patients admitted to the emergency department with non-severe community acquired pneumonia that 34% of these patients developed AKI many of whom never required admission to an ICU [6]. This suggests that AKI is not only related to shock states or critical illness, and that patients with non-life-threatening infections may also be at high risk of developing renal dysfunction and its short and long-term consequences.

Novel Concepts in the Pathophysiology of Sepsis-Induced AKI

Recent evidence suggests that the origin of most cases of AKI is multifaceted and that several, concurrent mechanisms may be at play. These mechanisms include inflammation, profound, heterogeneous distortion of microvascular flow at the peritubular and glomerular levels, and tubular epithelial cell injury and impairment. Given that these three major events occur early in the course of sepsis, and that cell death seldom occurs, we conceptualize early sepsis-induced AKI as the clinical and biochemical manifestation of tubular cell responses to injury. We further hypothesize that such response is, at least in part, adaptive in that it is driven by metabolic down-regulation and reprioritization of energy expenditure to avoid energy

imbalance and favors individual cell survival processes (such as maintenance of membrane potential and cell cycle arrest), at the expense of organ function (i.e., tubular absorption and secretion of solutes).

The Renal Microcirculation during Sepsis-Induced AKI

Sepsis causes a profound alteration in microvascular blood flow distribution [12, 17]. Such alteration is characterized by an increase in the heterogeneity of regional blood flow distribution, a decrease in the proportion of capillaries with "nutritive" (or continuous) blood flow, and an increase in the proportion of capillaries with intermittent or no flow [12, 18]. The renal microcirculation is disturbed in a similar fashion, as has been recently described in different models of sepsis-induced AKI [11, 19, 20], even in the setting of normal or even increased RBF [21]. Multiple mechanisms seem to frame this characteristic microcirculatory derangement, including endothelial dysfunction, impaired red blood cell deformability, thinning and damage of the glycocalyx layer, increased leukocyte activation and recruitment, and activation of the coagulation cascade with fibrin deposition [18]. Importantly, these alterations in microcirculatory flow and endothelial function are thought to contribute directly to the development of organ dysfunction through multiple mechanisms.

Uncoupling of microcirculatory blood flow distribution from metabolic demand, with the creation of microvascular shunts, has been proposed to result in areas of hypoperfusion and hypoxia [22, 23]. In relation to this, the endothelium also provides an essential system of retrograde communication that allows the microcirculation to fine tune and couple blood flow distribution to metabolic demand, which is in essence the concept of regional autoregulation. Tyml et al. have shown that LPS-induced endothelial injury results in loss of such retrograde communication rate between microvessels 500 μm apart [23, 24], suggesting that sepsis may not only impair the response to vasoactive mediators but also, the capacity of peripheral microvascular beds to autoregulate.

Similarly, endothelial dysfunction results in increased vascular permeability and worsening interstitial edema [25, 26], with two important consequences. First, edema increases the diffusion distance oxygen has to travel to reach target cells [27] further creating areas at risk for hypoxia. Second, given that the kidney is an encapsulated organ, tissue edema contributes to increased venous output pressures, aggravating congestion and perpetuating microvascular perfusion alterations [28, 29].

Endothelial cells are also important determinants of vascular tone and play an important role in the responsiveness to vasoactive mediators [30]. Injury to the arterial and arteriolar endothelium has consistently shown to result in impaired responsiveness to vasoactive substances, which may explain the loss of vasomotor tone during sepsis.

Nitric oxide (NO) has also been shown to have a potential role in the genesis of microvascular dysfunction and in the pathophysiology of AKI. Although sepsis is characterized by global increased NO production [31], the expression of one of the

most important catalyzers of its production, inducible NO synthase (iNOS), is rather heterogeneous [31]. Accordingly, it is possible that the heterogeneous expression of iNOS may result in heterogeneous regional concentrations of NO, which could result in the presence of vascular beds deprived of NO even in the setting of elevated systemic levels [32]. This is important as it is reminiscent of the characteristic heterogeneous pattern of microvascular dysfunction described in sepsis, and may relate pathophysiologically with areas of shunting and hypoxia [32]. Importantly, selective inhibition of iNOS not only can restore the renal microcirculatory derangements during sepsis, but is also associated with decreased functional manifestations of renal injury, suggesting that microcirculatory abnormalities may be in the mechanistic pathway of sepsis-induced AKI [19]. However, the interactions between NO, microvascular dysfunction, and AKI are not straightforward, as sepsis is also known to result in iNOS-dependent decrease in endothelial-derived NO synthase activity, which will also alter microvascular flow homeostasis [33, 34].

During sepsis, inflammation, oxidative stress, and the uncoupled eNOS [35] not only induce endothelial cell dysfunction but also damage the glycocalyx. The glycocalyx is a layer of organized glycosaminoglycan branches that protrudes from the surface of the endothelial cell membrane into the capillary lumen, and that has important biomechanical functions including maintenance of adequate capillary flow, oncotic and hydrostatic pressure gradient balance to limit filtration, and avoiding red and white cell adhesion [36]. Damage of the glycocalyx is thought to result in capillary leak, altered red blood cell flow, and increased adhesion and rolling of leukocytes after endothelial adhesion molecules are exposed, all of which contribute to the microvascular dysfunction phenotype characteristic of sepsis and to further inflammation.

Finally, sluggish peritubular flow may also result in amplification of the inflammatory signal. As demonstrated by Goddard et al. [37] in myocardial capillaries during a porcine model of endotoxemia, leukocytes decrease their velocities and increase their transit time in these areas of sluggish flow. In addition, there is evidence of upregulation of inflammatory molecules, such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 [38, 39] in these peritubular capillaries that would contribute to leukocyte activation and prolonged leukocyte transit. This prolonged transit may directly translate into a greater time of exposure of the endothelium and neighboring tubular epithelial cells to activated, cytokine secreting leukocytes and to other pathogen and damage-associated molecular patterns (PAMPs and DAMPs, respectively) that ultimately amplify the inflammatory signal, and induce focal oxidative stress and tubular injury. The tubular epithelial cells exposed to this amplified signal then act as primary targets for this alarm, and trigger a response in the adjacent segments of the proximal tubule evidenced by the induction of oxidative stress and vacuolization. The lack of apoptosis and necrosis suggests this is an organized, adaptive response that ultimately signals other tubular cells to shut down in a paracrine fashion. Importantly, this provides an explanation for why only a few heterogeneous groups of tubular epithelial cells demonstrate the typical histopathologic changes.

Inflammation Propagates Renal Damage During Sepsis

A strong association between cytokine levels (interleukin (IL)-6, IL-10, and macrophage migration inhibitory factor) and the development of sepsis-induced AKI [6, 40] supports the hypothesis that systemic inflammation is an important mediator of this process. During sepsis, although the inflammatory response is fundamental to clear the infection and later promote tissue recovery, it can also result in tissue damage and organ dysfunction [41]. In addition to leukocytes, dendritic cells, and resident macrophages, tubular epithelial cells are capable of recognizing and responding to pathogens-associated molecular patterns (PAMPs) through pattern-recognition receptors including toll-like receptors (TLR), C-type lectin receptors, retinoic acid inducible gene 1-like receptors, and nucleotide-binding oligomerization domain-like receptors [42], which results in the up-regulation of inflammatory gene transcription and initiation of innate immunity. This response is also stimulated by endogenous substances released by injured cells and tissues known as damage-associated molecular patterns (DAMPs), which include DNA, RNA, histones, HMGB1, and S100 proteins, and which are recognized by these same receptors [43].

Pro-inflammatory mediators activate endothelial cells and induce up-regulation of adhesion molecules like E-selectin, which has been demonstrated to play a major role in leukocyte recruitment into the kidney during the late stages of sepsis-induced AKI [44]. Although not seen in all models of sepsis-induced AKI [45], elimination of neutrophils or blocking adhesion molecules that are required for neutrophil recruitment into the kidney completely abolished sepsis-induced AKI in a cecal ligation and puncture (CLP)-induced sepsis model [44]. This observation can be explained by the fact that leukocytes leaving peritubular capillaries have a close proximity to tubular epithelial cells and can directly activate tubular epithelial and dendritic cells by releasing pro-inflammatory mediators and DAMPs. The cycle is then perpetuated by the release of mediators like leukotriene B_4, and platelet-activating factor which increase vascular permeability and up-regulate the expression of adhesion molecules that promote further inflammation [46–48]. In addition, DAMPs, PAMPs, and pro-inflammatory cytokines that are readily filtered through the glomerulus can activate these tubular epithelial cells from within the tubule (Fig. 8.1) [46, 49]. It has been recently shown that mammalian tubular epithelial cells (including human) express TLR2 and TLR4, and that these cells are capable of recognizing inflammatory mediators such as lipopolysaccharide (LPS) in a TLR4-dependent manner [50–53]. Furthermore, Krüger et al. [50] demonstrated that damaged human tubules stain positively for the TLR4 ligand, HMGB1, and that in vitro stimulation of human tubular epithelial cells with HMGB1 stimulates pro-inflammatory responses through TLR4 [50], suggesting that such mediators can act in an autocrine and paracrine fashion and may contribute to further tubular cell damage. The recognition that tubular epithelial cells are actually equipped with machinery to recognize the inflammatory signal supports the hypothesis that their response may be organized and not random. In support of this, Kalakeche et al. [51] have elegantly shown that TLR4-dependent LPS recognition in the tubular epithelial cells occurs in the S1 segment of the proximal tubule, that assembly of LPS with

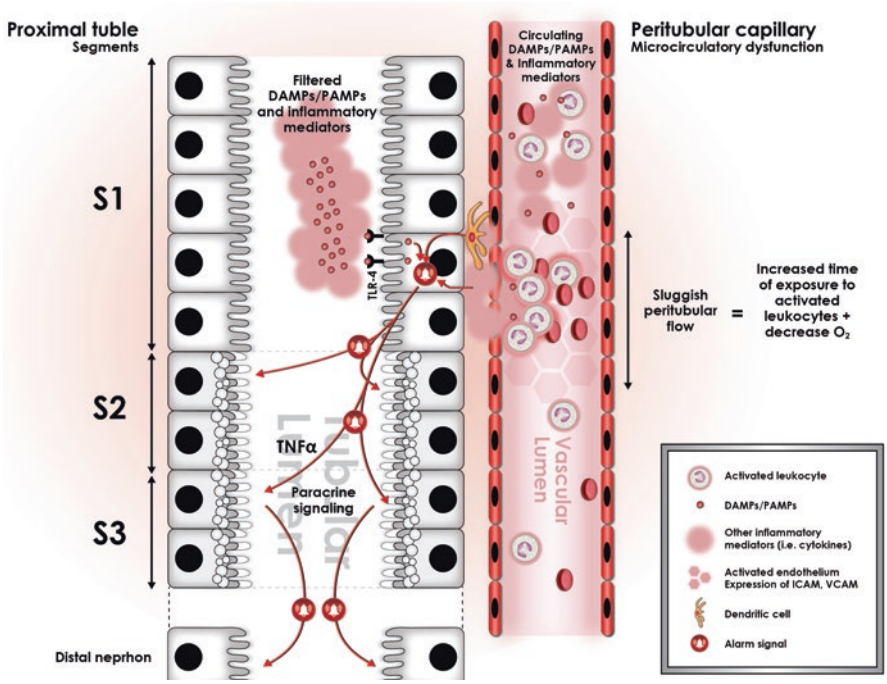

Fig. 8.1 Alterations in the Kidney During Sepsis. These alterations are characterized by increased heterogeneity of flow, as well as an increase in the proportion of capillaries with sluggish or stop flow (represented in the figure by *darker hexagons* in the peritubular capillary). We have conceptualized that these areas of sluggish peritubular flow increase the transit time of activated leukocytes and that this may set the stage for an amplification of the "danger signal" in such areas. Note that the expression of TNF receptors in the S2 segment tubular cells has led to the hypothesis that S1 cells may actually signal distal segments in a paracrine fashion through secretion of TNF. Finally, there are also data suggesting that this paracrine signal may include mediators of cell cycle arrest, namely, TIMP-2 and IGFBP-7. Source: Gomez et al. *Shock*. 2014;41:3–11

TLR-4 in the tubular epithelial cell produces internalization of LPS through fluid-filled endocytosis, and that this triggers an organized oxidative outburst in epithelial cells of the adjacent tubular segments (S2 and S3) but not in the S1 segment. These findings have led Kalakeche et al. [51] to suggest that the S1 segment of the proximal tubule may act as a sensor of danger that activates a series of events resulting in oxidative stress within distal tubular segments (S2, S3) and that could potentially explain tubular dysfunction in the setting of sepsis.

The (Adaptive) Responses of Tubular Cells to Inflammation

With the exception of T lymphocytes and intestinal epithelia, and despite multiple triggering stimuli [54], significant necrosis or apoptosis does not occur during sepsis [8, 9], which suggests that during the acute phase, regardless of the consequences

at the organ level, the cellular response is successful at preventing death. This denotes a possible underlying adaptive mechanism [9, 46, 55], and an opportunity to understand the response of the tubular epithelial cells to sepsis. Accordingly, it is reasonable to think that the tubular epithelial cell response to injury may be characterized at least in part by processes that limit pro-apoptotic triggers, by (a) prioritizing energy consumption and maintaining energy homeostasis, (b) maintaining cellular organelle function through quality control processes (general autophagy and mitophagy), and (c) limiting cell cycling and DNA replication.

Repriotitization of Energy Consumption

Energy balance dysregulation and mitochondrial injury are two major triggers of apoptosis and consequently, two of the most highly regulated cellular defense mechanisms to injury [56]. Although still controversial, sepsis seems to be associated with maintenance of ATP levels in the kidney [57] albeit with a decrease in production [58, 59], suggesting a significant decrease in ATP utilization. Furthermore, analogous to the evolutionarily conserved defense response to hypoxia, where nonvital functions are limited to avoid overtaxing energy expenditure [56], sterile inflammation by administration of lipopolysaccharide has been shown to induce downregulation of renal tubular cell ion transporters [60], which account for more than 70% of ATP cellular consumption [61]. Furthermore, there is evidence that experimental sepsis induces similar effects. Gupta et al. [62] showed that, in the presence of LPS, proximal tubules of mice have a delayed uptake of low-molecular-weight dextran, a sign of reduced endocytic capacity. Good et al. [63] have shown in an LPS-induced rodent sepsis model that LPS inhibits NHE1 (Na+/H+ exchanger 1) and thus blocks bicarbonate reabsorption in the medullary thick ascending limb of the loop of Henle. Finally, Hsiao et al. have shown that sodium transport (tubular sodium reabsorption) is decreased as early as 9 h after induction of sepsis by cecal ligation and puncture [64]. Taken together this evidence suggests that during sepsis, the response of the tubular epithelial cell may be characterized by an organized, hierarchical downregulation of major energy sinks like ion transport, while only fueling processes necessary to cell survival (i.e., maintenance of membrane potential) [65]. This is a highly conserved mechanism across species that seems to frame the core strategy of cellular response to threatening circumstances. It also provides the conceptual ground to suggest that cellular metabolic downregulation and reprioritization of energy consumption are pillars of the tubular epithelial response to sepsis and furthermore explains why organ function may be sacrificed in benefit of individual cell survival [62, 63].

Mitochondrial Quality Control Processes: Mitophagy

Mitophagy is an evolutionarily conserved, quality control mechanism, by which eukaryotic cells remove and digest dysfunctional mitochondria from the cytoplasm [66, 67]. During sepsis, TLR-mediated inflammation [68], oxidative stress [69, 70], and alterations in the electron transport chain that uncouple respiration and depolarize the mitochondrial membrane are potent triggers of mitophagy [67]. This early mitochondrial uncoupling characterized by an increment in O_2 consumption (VO_2) is not to be confused with the adaptive response it triggers, which is framed by the activation of mitophagy, and is characterized by a decrement in VO_2 and conservation of energy. In the kidney, mitophagy is activated as early as 3 h after CLP-induced sepsis [64], suggesting it is part of the early response of tubular epithelial cells to injury. Importantly, insufficient activation of mitophagy has been associated with worse outcome in critically ill patients, and it has been postulated to contribute to cell and organ dysfunction [71]. On the other hand, stimulation of autophagy has been shown to be effective at protecting cells [64] and organ function [71] in the setting of experimental inflammatory insults. Furthermore, in the setting of experimental sepsis induced by CLP, decreased autophagy has been associated with increased blood urea nitrogen and creatinine levels and a decline in proximal tubular sodium transport [64]. As a protective response, mitophagy offers several advantages, namely, removal of dysfunctional mitochondria, with subsequent decrement in ROS/RNS production, energy conservation, limiting oxidative stress damage, and importantly, intercepting proapoptotic signals at the mitochondrial level impeding triggering of apoptosis [67, 72–74]. Indeed, Carchman et al. have shown that inhibition of mitophagy results in a robust apoptotic signal in hepatocytes of animals subjected to CLP [58]. It is unknown, however, what mitophagy-induced maintenance of renal function really means. The adaptive response, framed by metabolic downregulation, would most likely decrease tubular and renal function and not promote it, just as hibernation promotes the loss of function. Indeed, increased or preserved renal function in the setting of stress may result harmful in the long run. Yet, animal and human data associate acute stimulation of autophagy with preserved renal function, and its faulty activation or decline with worse outcome. It is possible that the interplay of autophagy and tubular cell function varies with time and that persistence of the initial protective response may ultimately be deleterious in the subacute or chronic phases.

Cell Cycle Arrest

There is a growing body of evidence indicating that mitochondria are intimately involved in the regulation of the cell cycle [67]. The ability of mitochondria to move within the cell, change shape, and coalesce in different ways has recently emerged

as an important feature, which may influence the cell cycle [75]. Briefly, the cell cycle is the progression of cells through a number of steps in preparation for mitosis (G0, G1, S, G2, M). This preparation portrays several checkpoints in which the cell seems to evaluate whether it is prepared to advance to the next phase. Of particular interest to renal tubular injury in sepsis and the involvement of mitochondrial regulation is the G1-S checkpoint. Only at and during this stage, mitochondria have been shown to coalesce into a single, tubular network of mitochondria. This mesh seems to act as syncytia, with electrical coupling and unusual hyperpolarization [76], which fits well with prior studies showing an increase in O2 consumption during the G1-S transition of the cell cycle [77]. This also relates to the finding that a reduction in ATP production induced by specific ETC mutations produces cell cycle arrest at the G1-S checkpoint [78]. Together, these data indicate that the formation of this giant tubular network is necessary to meet the energy requirement needed to synthesize all the components for adequate cell division. It also suggests that the G1-S border is an important checkpoint of the cycle, whereby the inability to meet such energy requirements induces cell cycle arrest presumably to prevent a potentially lethal energy imbalance [75]. Yang et al. [79] recently showed in a rodent model of CLP-induced sepsis that G1-S cell cycle arrest was associated with kidney injury and that recovery of renal function paralleled cell cycle progression 48 h after CLP. These findings have become even more clinically relevant as tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7), two markers involved in G1-S cycle arrest, have been identified as the most sensitive and specific markers to predict risk of development of AKI in critically ill patients [80–82]. We speculate that the renal cell cycle arrest in the epithelial tubular cell may provide an advantage by avoiding replication because (a) it conserves energy and prevents triggering apoptosis or necrosis and (b) limiting replication diminishes the probability of DNA damage, reducing not only energy consumption employed in DNA repair, but also decreases the chances of triggering apoptosis.

Potential for Diagnostic and Therapeutic Targets

To date, no therapeutic measures are available to prevent or treat sepsis-induced AKI. A potential reason for this may be that often therapy is started too late in the disease process. The development of new biomarkers, which also provide insights into the pathophysiology of the disease, makes it possible to detect kidneys at risk for injury and thus enable earlier initiation of interventions [80–82].

The knowledge that inflammation, microvascular dysfunction, and adaptive responses of tubular cells are involved in the development of sepsis-induced AKI provides new diagnostic and therapeutic avenues. As these mechanisms are closely interlinked with each other, modulating one of these components simultaneously alters other components. As increased levels of pro-inflammatory mediators (e.g., IL-6) are associated with the development of AKI [40], it is tempting to speculate

that eliminating these mediators or endotoxin can prevent sepsis-induced AKI. Experimentally, it has been shown that removal of such mediators by hemoadsorption completely protects against AKI in a CLP model of sepsis [7, 83, 84], and a clinical study demonstrated that reducing endotoxin by polymyxin-B hemoperfusion reduced RIFLE scores and urine tubular enzymes [7]. Along the same lines, Alkaline phosphatase (AP) is an endogenous enzyme that exerts detoxifying effects through dephosphorylation of endotoxins and pro-inflammatory extracellular ATP and is reduced during systemic inflammation. Heemskerk and colleagues [85] demonstrated that administration of AP was associated with a decreased expression of iNOS synthase in proximal tubule cells isolated from urine and that this related to an attenuated urinary excretion of glutathione *S*-transferase A1-1, a proximal tubule injury marker. In a small, randomized trial, Pickkers et al. showed that the administration of exogenous AP in septic patients improved endogenous creatinine clearance and reduced the requirement and duration of renal replacement therapy [86]. Modulating TNF-α signaling might be yet another therapeutic option, because a polymorphism in the promoter region of the TNFA gene is associated with markers of kidney disease severity and distant organ dysfunction [87].

To improve microcirculatory perfusion, vasodilators in the setting of sepsis are currently under investigation including nitroglycerin [17, 88], NO administration, and modulation of NO production [32, 34]. Furthermore, drugs with pleiotropic effects on the vasculature, such as statins [89] and erythropoietin [90], have the potential to prevent kidney injury by enhancing eNOS expression and decreasing vascular permeability. However, it is important to consider that regional microcirculatory autoregulation is only possible if sufficient perfusion pressure is attained, and thus early resuscitation goals still need to focus on achieving a mean arterial pressure sufficient enough to ensure perfusion. Asfar et al. have shown that such a goal must be a mean arterial pressure of 65–70 mmHg, and that higher levels of MAP only result in improved outcomes (decreased need for RRT) in the subpopulation of patients with chronic hypertension [91].

However, it is important to explore these treatment options bearing in mind that these mechanisms are part of the natural host response to sepsis, and that although known perpetrators of injury, they are also necessary for bacterial clearance, tissue protection and repair, and ultimately survival. Accordingly, the reader must not expect a single treatment modality to emerge as a magic bullet to prevention and/or treatment sepsis-induced AKI.

Conclusions

Close examination of the histology of various organs of patients dying from sepsis has dramatically changed the way we think of sepsis-induced organ dysfunction. The recognition that in the case of the kidney, sepsis-induced AKI cannot be entirely explained by the traditional concept of acute tubular necrosis, and that sepsis does not cause overt apoptosis and necrosis in failing organs, has challenged the notion

that ischemia is the only mechanism explaining organ dysfunction. Importantly, it has also prompted many to suggest that the response to the septic environment may early on be adaptive in nature. In this review, we have now put forth a conceptual model that cellular energy regulation is fundamental to the adaptive response, and that such regulation is driven at least in part by metabolic down-regulation and re-prioritization of energy utilization and by mitochondrial quality control processes like mitophagy. Further work is warranted to better understand the role, timing, and reach of these multiple mechanisms in the pathogenesis of sepsis-induced AKI, and if this can be translated into novel diagnostic and therapeutic interventions to improve outcome in this patient population.

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