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Full Review

Emerging role of Lipopolysaccharide binding protein in sepsis-induced acute kidney injury

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ABSTRACT

Sepsis remains a serious cause of morbidity and mortality in critically ill patients, with limited therapeutic options available. Of the several disorders connected with sepsis, acute kidney injury (AKI) is one of the major complications. The pathophysiology of sepsis-induced AKI is characterized by severe inflammation in renal parenchyma with endothelial dysfunction, intra-glomerular thrombosis and tubular injury. Endothelial dysfunction is regulated by several mechanisms implicated in cellular de-differentiation, such as endothelial-to-mesenchymal transition (EndMT). Gram-negative bacteria and their cell wall component lipopolysaccharides (LPSs) are frequently involved in the pathogenesis of AKI. The host recognition of LPS requires a specific receptor, which belongs to the Toll-like receptor (TLR) family of proteins, called TLR4, and two carrier proteins, namely the LPS-binding protein (LBP) and cluster of differentiation 14 (CD14). In particular, LBP is released as a consequence of Gram-negative infection and maximizes the activation of TLR4 signalling. Recent findings regarding the emerging role of LBP in mediating sepsis-induced AKI, and the possible beneficial effects resulting from the removal of this endogenous adaptor protein, will be discussed in this review.

Keywords: endothelial dysfunction, LPS-binding protein, renal fibrosis, sepsis-induced acute kidney injury, tubular maladaptive response

INTRODUCTION

Sepsis is a complex disorder characterized by a dysregulated host response to an active infection, which is enhanced by invading microorganisms or their products [1, 2]. Pathogen recognition is mediated by specific receptors, called Toll-like receptors (TLRs), which are expressed on immune and non-immune cells [3]. TLRs, in concert with other pattern recognition receptors (PPRs), can amplify the inflammatory response by binding endogenous ligands: damage-associated molecular pattern molecules that are released from injured cells [2]. This overwhelming response leads to the loss of the normal balance between pro-inflammatory and anti-inflammatory mechanisms and may predispose an individual to the development of multiple organ dysfunction syndrome (MODS). Kidneys are frequently involved in MODS, with a high incidence of acute kidney injury (AKI) [2]. However, the pathophysiology of sepsis-induced AKI remains incompletely understood. Recent findings have identified an entire 'orchestra' of adaptive and maladaptive cellular mechanisms that give rise to intra-renal haemodynamic changes, infiltration of inflammatory cells in the renal parenchyma, endothelial dysfunction and tubular injury [2].

Endothelial cells (ECs) are considered to be one of the principal cellular targets in AKI, as they can lose their common regulatory functions and acquire a dysfunctional phenotype [4]. The endothelial-to-mesenchymal transition (EndMT),

one of the most interesting pathogenic processes, can affect endothelial plasticity, which contributes to a fibroblast-like phenotype being conferred to ECs [5, 6]. With the induction of EndMT, significant alterations in vessel function can potentially contribute to the development of renal fibrosis. Like ECs, tubular epithelial cells not only develop apoptosis or necrosis during sepsis-induced AKI, but also gain an adaptive response regulated by the mitochondria [2, 7].

Among the different pathogens, Gram-negative bacteria are frequently implicated in sepsis-induced AKI, with lipopolysaccharides (LPSs) playing a major role [8]. LPS are recognized by TLR4, which is constitutively expressed in kidney cells such as tubular epithelial cells and ECs [2, 9]. The cellular response to endotoxins requires a carrier protein, the LPS-binding protein (LBP), to facilitate the transfer of LPS to TLR4 [10, 11]. Despite recent insights into the pathogenesis of sepsis-induced AKI, therapeutic approaches need to be improved [12]. On the other hand, increasing evidence suggests a promising role for blood purification techniques [13, 14]. In this review, we summarize recent data on the pathogenesis of sepsis-induced AKI by focussing on the role of LBP in the host response to endotoxins and possible therapeutic interventions.

PATHOPHYSIOLOGY OF SEPSIS-INDUCED AKI: ROLE OF THE LPS–TLR4 AXIS

For several years, sepsis-induced AKI has been considered to be the final result of low cardiac output with decreased renal blood flow; this was associated with increased renal vascular resistance leading to tubular cell hypoxia and acute tubular necrosis. This hypothesis, called the 'ischaemia paradigm', was based on the concept that renal hypoperfusion was the main cause of acute tubular necrosis. However, this concept has been disproved by several studies demonstrating that sepsis-induced AKI is characterized by hyperdynamic circulation associated with an exacerbated inflammatory response, without significant evidence of acute tubular necrosis [15]. In this complex scenario, invading microorganisms or their products (such as LPSs), which are identified via pathogen-associated molecular patterns (PAMPs), activate immune cells and renal resident cells via a large spectrum of PPRs, including TLRs [2, 3]. Among the TLRs, TLR4, TLR2 and TLR9 appear to be important in septic AKI [16]. In particular, TLR4 has also been found on ECs and on both distal and proximal tubular cells in the kidney, suggesting a pivotal role for it in mediating renal injury [1, 2, 9].

Endotoxemia usually results in the impairment of renal function [17]; the mechanisms involved are attributed to LPS, a critical structural component of the outer wall of Gram-negative bacteria [8]. LPSs, also known as endotoxins, are defined as the main PAMPs, and TLR4 has been identified to be the specific receptor for LPS signalling [18]. The recognition of endotoxins by the host requires a carrier, known as LBP. LBP takes LPS molecules to the cellular surface, forming a ternary complex with cluster of differentiation 14 (CD14), which is present as a membrane-bound glycosylphosphatidylinositol (GPI)-anchored protein (membrane-bound CD14). CD14 can also be found in a soluble form, generated by proteolytic cleavage, that lacks the GPI anchor. In contrast to monocytes and macrophages, the cellular membrane of EC does not contain membrane-bound CD14, and this cell type is dependent on soluble CD14 [18]. Like LBP, CD14 facilitates the transfer of LPS to the receptor complex formed by TLR4 and the MD2 adaptor protein [19]. After LPS binding (Figure 1, left panel), TLR4 forms homodimers through binding of cytoplasmic tails and activates a signalling cascade recruiting the adaptor proteins, TIRAP [Toll-Interleukin-1 receptor (TIR) domain containing adaptor protein] and TRAM [TIR-domain-containing adapter-inducing interferon-β (TRIF)-related adaptor molecule], through the interaction of TIR domains between the receptor and cytosolic adaptors. Activation of TLR4 leads to the stimulation of both Myeloid differentiation primary response gene 88 (MyD88)-dependent and MyD88-independent pathways [19]. In the MyD88-dependent pathway, Interleukin-1 receptor-associated kinase (IRAK)1 and IRAK4 can activate TNF-α receptor associated kinase factor 6 (TRAF66), leading to the downstream activation of the IκB kinase (IKK) complex, mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt pathways. The activation of IKK results in the phosphorylation and degradation of Inhibitor of kappa B (IκB), allowing the nuclear translocation of nuclear factor- kappa B (NF-κB), and induces the transcription of pro-inflammatory molecules. Furthermore, PI3K activates Akt, leading to IKKβ phosphorylation of p65 and subsequent activation of NF-κB. Induction of the MAPK pathway, c-jun NH(2)-terminal kinase (JNK) in particular, activates the transcription factor AP-1, which has a pivotal role in regulating the release of pro-inflammatory cytokines. Interestingly, NF-κB and MAPK can also be activated in MyD88-deficient macrophages, suggesting that MAPK and NF-κB can also be induced through a MyD88-independent pathway. The MyD88-independent pathway induces the expression of Interferon (IFN)-inducible genes through activation of the transcription factor IFN regulatory factor 3 (IRF3) [19].

ROLE OF LBP IN TLR4 SIGNALLING

Known as an acute phase protein, LBP is synthesized by hepatocytes and released into the bloodstream as a consequence of Gram-negative bacterial infection [11]. LBP is capable of extracting and transferring endotoxin monomers from the bacterial outer membrane or LPS aggregates to the CD14 protein. Next, CD14 delivers endotoxin monomers to MD2–TLR4, activating LPS signalling (Figure 1, left panel).

During an acute inflammatory response, LBP levels increase and maximize the host response to infection, even at low concentrations of endotoxin [10, 20]. Similarly, serum concentrations of soluble CD14 are elevated in the first phase of sepsis to prevent widespread infection [21, 22]. Interestingly, patients with high levels of LBP are prone to prolonged inflammation, MODS and an increased risk of mortality [23, 24]. In addition, several organs, including the lungs, kidneys and liver, can contribute to the synthesis of LBP and CD14, amplifying the local production of inflammatory cytokines [25, 26].

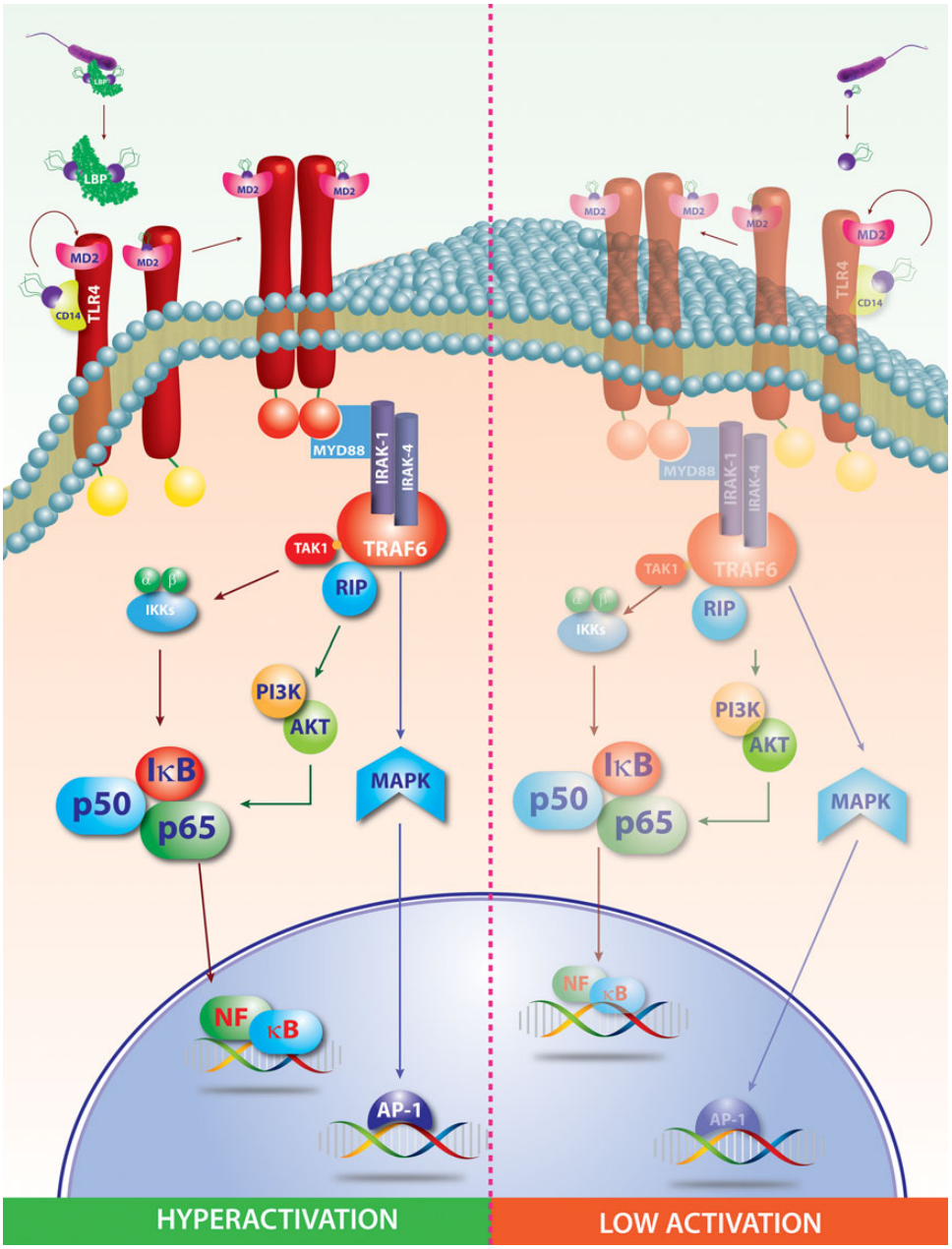

FIGURE 1: Role of LBP in TLR4 activation. Endotoxin monomers are extracted from bacterial membranes and transferred to CD14 by LBP in order to enhance TLR4 activation. The presence of LBP increases the host response, amplifying LPS signalling (picture on the left). The removal of LBP leads to a significant decrease of endotoxin binding, causing a shutdown of downstream pathways involved in TLR4–LPS signalling (faded image on the right).

RENAL TUBULAR DYSFUNCTION IN SEPSIS-INDUCED AKI

During sepsis, the pro-inflammatory renal microenvironment plays a pivotal role in causing tubular dysfunction. The most relevant morphological change observed in the proximal and distal tubule is cellular shedding, characterized by cellular desquamation with a loss of barrier function and increased permeability, resulting in the leakage of glomerular filtrate from the tubular lumen to the interstitium [27]. Several authors have agreed on the prominent role of tubular apoptosis rather than necrosis (Table 1) in the pathophysiology of this process [28], caused by altered mitochondrial activity with subsequent failure of energy status [29]. In contrast, histological evidence makes it unlikely that the occurrence of intense tubular apoptosis in patients with sepsis-induced AKI can be confirmed. It has been hypothesized that an excess of inflammatory cytokines may potentiate the intracellular events that lead to an acceleration of the apoptotic process, which becomes difficult to detect. Nevertheless, recent clinical studies have demonstrated that plasma from septic patients with AKI contains pro-apoptotic factors [30, 31]. Interestingly, we recently showed that apoptosis is present in the early phase of LPS-induced AKI and is characterized by caspase-3 positive tubular epithelial cells [5]. In addition, tubular dysfunction is not only associated with apoptosis, but probably

also with the epithelial-to-mesenchymal transition (EMT) [32]. This process allows tubular cells to acquire a mesenchymal phenotype, with consequent overproduction of pro-fibrotic agents contributing to chronic kidney disease (CKD) [33].

In this context, little is known about the involvement of LBP in tubular dysfunction. As shown in Table 1, LBP mRNA was detected in the epithelial cells of the proximal tubules, suggesting that this portion of the kidney might be associated with a local inflammatory response during pyelonephritis [26]. Bussolati *et al.* [34] demonstrated that, in the presence of both soluble CD14 and LBP, proximal tubular cells were up to 100 times more sensitive to LPS activation, even at lower LPS concentrations; the presence of soluble CD14 and LBP was also required for the induction of apoptosis in tubular cells [34]. These observations highlight the crucial role of LBP acting as a sensor of circulating endotoxins, supporting LPSs internalization and enhancing the apoptotic pathway [29].

ENDOTHELIAL DYSFUNCTION IN SEPSIS-INDUCED AKI

ECs constitute the inner lining of the vessels and play a key role in regulating vascular tone, barrier permeability, activation of coagulation and the balance between pro-inflammatory and anti-inflammatory mediators [35]. During sepsis, the endothelium is considered to be one of the main targets of the exacerbated inflammatory response. ECs lose their functions and switch from a quiescent to an active state [4]. Commonly, microbial products, and in particular LPSs, directly activate ECs by binding to membrane TLRs [36]. Interestingly, data on the effects of LPS on ECs are still conflicting, as some report pro-inflammatory and pro-apoptotic effects [37], while others show cytoprotective/antiapoptotic effects (Table 1) [38, 39]. Effectively, TRAF6 acts as a bifurcation point of the LPS-initiated death and survival signals [40]. We recently demonstrated the survival of ECs upon LPS activation in a swine model of sepsis-induced AKI [5]; ECs initiated a survival-signalling pathway displaying an abnormal phenotype. This phenotypic change is commonly described as a severe form of endothelial plasticity known as EndMT (Table 1, Figure 2) [41].

EndMT: AN UNEXPLORED TARGET IN AKI

The origin of renal fibroblasts is an interesting issue, and recent evidence has suggested that the involvement of EndMT is crucial in renal fibrosis [4]. This mechanism was first described in

Table 1. Comparison of LPS effects on endothelial and tubular epithelial cells

	Endothelial cells	Tubular cells
Survival/apoptosis ratio	Both pro-inflammatory/pro-apoptotic and cytoprotective/antiapoptotic [38–40]	Severe apoptosis rather than necrosis [28, 29, 31]
Morphological changes	Endothelial dysfunction and EndMT: upregulation of fibroblast markers, downregulation of endothelial markers and migratory capacity [4–6]	Shedding, vacuolization and lack of brush border; irreversible mitochondrial dysfunction and oxidative stress [53, 61, 62]
Pathological effects	Development of fibrosis [5, 6]	Source of local inflammation [29, 30]
Receptor activated	TLR4 [18]	TLR4 and TNF-α receptor [30]
Principal pathways involved	Activation of PI3K/AKT [37]	Activation of NF-κB [29] and TNF- α [30, 63]
LBP expression	No local LBP expression [18]	LBP mRNA expression [26]
LBP effects	LBP enhances the uptake of LPS and mediates endothelial dysfunction [5, 34, 52]	LBP was required for apoptosis in tubular cells [34]

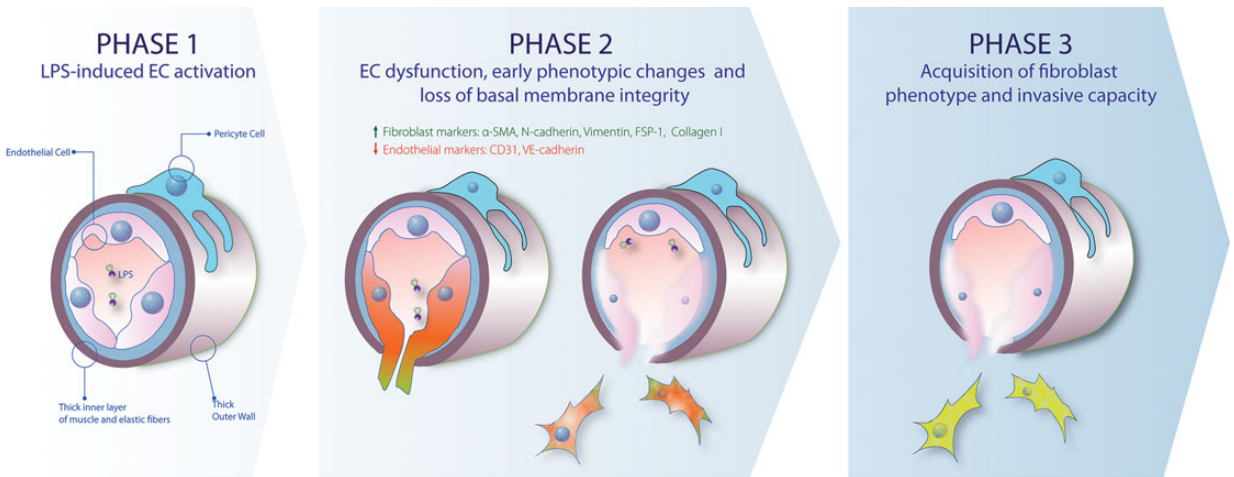

FIGURE 2: Schematic phases of LPS-induced EndMT. Activation of ECs after LPS binding to TLR4 causes phenotypic changes, with a decrease of endothelial markers and gain of fibroblast markers (left panel). The acquisition of a fibroblastic phenotype is accompanied by the loss of basal membrane integrity of the vascular wall (central panel). These dysfunctional cells, differentiated into myofibroblasts, migrate to the interstitium and contribute to tissue fibrosis (right panel).

embryonic heart development studies, but was later also reported in studies related to pathological conditions such as cardiac fibrosis [42, 43] or the generation of carcinoma-associated fibroblasts. Over the last few years, several studies in animal models of CKD have demonstrated, for the first time, the contribution of EndMT in the progression of renal fibrosis associated with CKD [44]. In mice and swine models of ischaemia–reperfusion injury, we and others have shown that EndMT can also be detected in the early phase of AKI [45, 46]. Of the different factors involved in the progression of renal fibrosis, TGF-β is the most potent inducer of EndMT [47]. ECs exposed to LPS undergo the same phenotypical changes as TGF-β-treated cells, highlighting the potential role of LPS in inducing EndMT [48]. We recently demonstrated the occurrence of EndMT in an animal model of sepsis-induced AKI [5]. After LPS stimulation (Figure 2), ECs lost their specific markers, CD31 and vascular endothelial (VE)-cadherin, and acquired fibroblast markers such as α-smooth muscle actin (SMA), vimentin, N-cadherin and Fibroblast-specific protein (FSP)-1. These transitioning cells detach from the intima of the vascular wall and migrate into the interstitial space, differentiating in activated myofibroblasts and contributing to the mechanism of fibrogenesis (Figure 2). Following this hypothesis, we observed the occurrence of EndMT [5] through the co-localization of CD31 and α-SMA markers in endotoxemic vessels (Figure 3A) and peritubular capillaries (Figure 3B). Confocal microscopy images and the relative cartoon in Figure 3A show transitioning $CD31^+/\alpha\text{-}SMA^+$ ECs that migrate from the intima to the medial layer of the vascular wall. Effectively, these dysfunctional ECs acquire migratory features and contribute, together with vascular smooth muscle cells, to the synthesis of different components of the extracellular matrix [41].

Several papers have described the invasive capacity of ECs after mesenchymal transition [6, 47]. In our model, we found intra-vessel migration of $CD31^+/\alpha\text{-}SMA^+$ ECs in the renal artery. It has been shown that smooth muscle cells are important sources of interleukins, chemokines and growth factors that induce pro-inflammatory and pro-migratory stimuli regulating EndMT [41]. However, we found that peritubular capillary ECs significantly altered their phenotype by acquiring α-SMA but did not show significant migration, at least in the first hours of LPS-induced AKI (Figure 3). Taken together, these data indicate that EndMT might be a pivotal pathogenic process in the development of renal fibrosis, not only in CKD but also in AKI [5].

DIFFERENT ORIGINS OF MYOFIBROBLASTS IN RENAL FIBROSIS

EndMT has been reported to be a source of myofibroblasts in renal diseases, but the extent of this contribution may vary

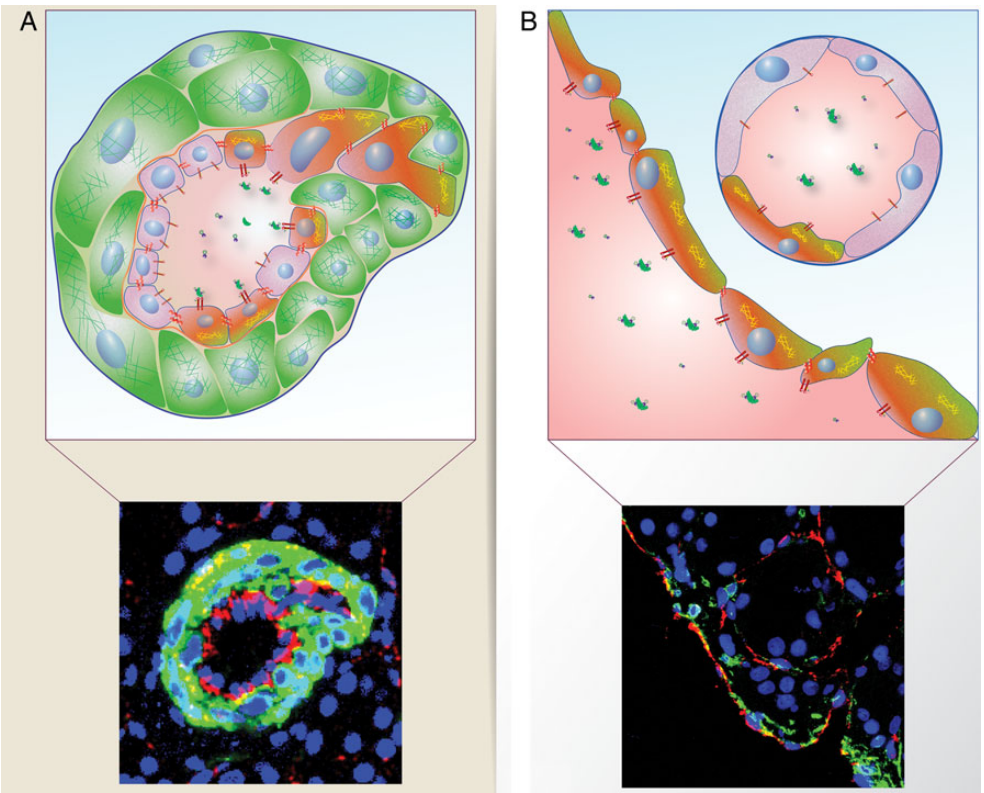

FIGURE 3: EndMT in LPS-induced AKI. Swine paraffin-embedded renal sections were double stained for CD31 (red) and α-SMA (green) to demonstrate the occurrence of EndMT. $CD31^+$ ECs acquired the α-SMA marker in both (**A**) large vessels and (**B**) peritubular capillaries. (A) Transitioning $CD31^+/\alpha\text{-}SMA^+$ ECs migrate from the intima to the medial layer of the vascular wall, acquiring invasive capacity. Cartoon of a renal vessel describing ECs activation by LPS, the acquisition of fibroblast markers (ECs stained in red, CD31 and green α-SMA) and their migration across the basal membrane. (B) In renal interstitium, ECs of peritubular capillaries co-express both CD31 and α-SMA markers but do not migrate from the capillary lumen. Moreover, in the corresponding cartoon, transitioning ECs are marked with both red and green colours to illustrate the EndMT process. Magnification: ×630. TO-PRO-3 was used to counterstain nuclei (blue).

depending on the model used and the stage of fibrosis [49]. Increasing evidence has helped to identify a heterogeneous group of cells that is able to contribute to generation of the population of interstitial myofibroblasts [50]. This group includes bone marrow-derived fibroblasts, tubular epithelial cells, ECs, pericytes and interstitial fibroblasts. Myofibroblasts are considered to be the key cellular effectors and the main producers of extra cellular matrix components during fibrosis. The various approaches used to identify the origin of myofibroblasts are based on the expression of differentiation markers and/or the labelling of progenitor cells followed by lineage tracing [49].

Interestingly, recent findings have demonstrated that pericytes also exhibit enormous plasticity and trans-differentiate into collagen-producing myofibroblasts [49]. Tubular epithelial cells promote this process, increasing TGF-β expression, which has been shown to activate the pericyte–myofibroblast transition [51]. Moreover, the detachment of pericytes from endothelial cells leads to capillary instability with an associated increase in the development of fibrosis.

The involvement of tubular cells in the generation of fibroblasts is still being debated. During sepsis-induced AKI, the acquisition of a fibroblast-like phenotype may be promoted by cell cycle arrest and the subsequent activation of JNK signalling, which in turn upregulates the production of pro-fibrotic cytokines [33]. In particular, uremic toxins such as indoxyl sulphate seem to mediate the increased expression of fibrosis-related genes, inflammatory mediators and chemokines in tubular cells [33]. Thus, numerous factors promote renal injury with the activation of epithelial cells, ECs and pericytes into fibrosis-producing myofibroblasts. These findings also suggest that specific therapies targeting epithelial cells, ECs and pericytes could minimize the fibrotic process and the subsequent loss of kidney function [51].

In addition to resident kidney cells, both mesenchymal stem cells and fibrocytes derived from haematopoietic stem cells can differentiate into myofibroblasts in response to profibrotic factors. In the context of renal diseases, the injection of GFP-positive bone marrow cells in bone marrow–depleted mice has shown that 15% of myofibroblasts derive from circulating cells, supporting the role of these cells in the pathogenesis of kidney fibrosis [49].

ROLE OF LBP IN SEPSIS-INDUCED ENDOTHELIAL DYSFUNCTION

Among the different factors involved in TLR4 signalling at the vascular level, LBP seems to have a crucial role in enhancing and amplifying the endothelial response to endotoxins. *In vitro*, LBP facilitates the uptake of LPS into human coronary artery ECs, even at low concentrations of endotoxins (Table 1). Blocking LBP strongly reduces LPS binding to TLR4 and the subsequent ECs activation [52]. Accordingly, we have found that the removal of LBP is critical for the prevention of endothelial dysfunction in a swine model of LPS-induced AKI, both *in vitro* and *in vivo* [5]. The *in vitro* supplementation of exogenous LBP-induced collagen I synthesis by ECs leads to the early development of EndMT [5]. The initiation of EndMT with newly generated renal myofibroblasts in the earliest phase of AKI might be a beneficial mechanism that attempts to repair the damage as it occurs. However, in the presence of persistent LPS activation, there might be a massive deposition of extracellular matrix components, tubular atrophy and dilatation, interstitial fibrosis and glomerulosclerosis with irreversible renal damage [53]. Therefore, we hypothesize that the generation of activated renal myofibroblasts by EndMT, throughout the LBP–LPS–TLR4 axis, may represent an important mechanism of renal fibrosis in sepsis-induced AKI. As described in Figure 1 (left panel), the presence of LBP increases the endothelial response by amplifying LPS signalling, which, as a result, leads to EndMT. On the basis of our observation [5], the removal of LBP (Figure 1, right panel) may significantly decrease the capacity of LPS to bind and activate the TLR4 receptor complex, with abrogation of the intracellular signalling that regulates endothelial dysfunction.

THERAPEUTIC PERSPECTIVES

Over the past decade, new therapies based on the employment of immune regulators have been adopted to abrogate the hyperinflammatory response in the first phase of this disorder. However, the use of this approach is controversial because protracted immunosuppression can induce the acquisition of a secondary infection in patients [12, 54]. Moreover, recent investigations into the effects of specific inhibitors on potential sites of LPS–TLR4 signalling have revealed insufficient abrogation of the endotoxin-associated inflammatory cascade [55]. Soluble receptors and monoclonal antibodies have been used to block the interaction of LPS and other ligands with TLR4, but have frequently acted as agonists without any efficacy [55].

Endotoxins, the principal triggers of the initiation and propagation of sepsis, might be important targets for immunotherapy. Low levels of LPS were detected in subjects with endotoxemia and septic shock, whereas high levels were found in patients with severe shock and at high risk of mortality [54]. Despite these differences, there was no correlation between LPS levels and clinical outcome, indicating that even low levels of LPS might be detrimental, since carrier factors such as LBP can aid the activation of TLR4 [54, 55]. At the cellular level, the endothelium is considered to be a potential target for new therapeutic approaches aimed at limiting endothelial dysfunction. Different strategies have been employed to attenuate the endothelial response in sepsis. One potential approach was the infusion of monoclonal antibodies to inhibit leukocyte–endothelium adhesion, but it caused platelet activation with consequent vascular obstruction and coagulation [56] and detrimental effects. Belcher *et al.* [60]reported a case of recovery of endothelial function through the infusion of a specific small-molecule inhibitor, TAK-242 (resatorvid) [57], which selectively binds the intracellular domain of TLR4 and causes the shutdown of intracellular signalling. Therefore, the identification of regulatory elements of TLR4 signalling in ECs may facilitate the development of novel therapies for sepsis.

Interestingly, new therapies have been developed for the treatment of sepsis-induced AKI through blood purification

via an extracorporeal circuit through a device (membrane, sorbent) where circulating inflammatory mediators and/or bacterial toxins can be removed, thereby modulating systemic inflammation [54, 58]. Recently, we have demonstrated that the removal of LBP by coupled plasma filtration adsorption (CPFA), rather than endotoxins, might prevent endothelial dysfunction during LPS-induced AKI [5]. CPFA is a blood purification technique in which the patient's blood circulates through a plasmafilter, which separates plasma from the blood and guides it through an adsorption resin cartridge [59], allowing the non-selective removal of inflammatory circulating mediators and the restoration of an adequate immune response. CPFA treatment has been shown to increase the responsiveness of leucocytes and monocytes to endotoxins, avoiding the risk of a secondary infection [59]. Moreover, this technique induces improvements in the haemodynamics of septic patients [60].

It is known that the CPFA adsorbent cartridge does not remove endotoxins from circulating blood. Our group recently showed that CPFA modulation of the host response to endotoxins is mediated by the removal of LBP [5]. In our experimental model, the decrease in LBP levels was associated with protective effects on the renal tissue, with prevention of endothelial and tubular dysfunction [5]. In particular, the removal of LBP impaired the development of EndMT and hampered the acute development of tubulo-interstitial fibrosis, suggesting a direct role of renal ECs activation in fibrogenesis through both direct and indirect mechanisms [5]. Microvascular rarefaction, together with progressive hypoxia and inflammation, represent the driving forces for matrix accumulation from resident fibroblasts. On the other hand, ECs may become a direct source of fibroblast cells through the EndMT process and collagen production [41]. Therefore, CPFA treatment may protect the renal parenchyma, preventing endothelial dysfunction and acute fibrosis in the course of AKI.

CONCLUSIONS

As discussed in this review, sepsis is a complex mosaic of interconnected events that leads to a high incidence of AKI in critically ill patients. Because of the pivotal role played by ECs in renal fibrosis, and their involvement in the initial stages of this disorder, in-depth investigations are necessary to find an adequate and targeted therapeutic intervention. Considering the significant inflammatory substrate of this disorder, the early removal of inflammatory mediators such as LBP may be crucial to improve the clinical outcome of critically ill patients by preventing sepsis-induced AKI.

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CONFLICT OF INTEREST STATEMENT

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