Role of heparanase in sepsis-related acute kidney injury (Review)

JIAN-CHUN LI[1], LIN-JUN WANG[1], FEI FENG[1], TING-TING CHEN[1], WEN-GUI SHI[2] and LI-PING LIU[3]

[1]The First Clinical Medical College of Lanzhou University; [2]Cuiying Biomedical Research Center, The Second Hospital of Lanzhou University; [3]Department of Emergency, The First Hospital of Lanzhou University, Lanzhou, Gansu 730000, P.R. China

Received January 4, 2023; Accepted June 8, 2023

DOI: 10.3892/etm.2023.12078

Abstract. Sepsis-related acute kidney injury (S-AKI) is a common and significant complication of sepsis in critically ill patients, which can often only be treated with antibiotics and medications that reduce S-AKI symptoms. The precise mechanism underlying the onset of S-AKI is still unclear, thus hindering the development of new strategies for its treatment. Therefore, it is necessary to explore the pathogenesis of S-AKI to identify biomarkers and therapeutic targets for its early diagnosis and treatment. Heparanase (HPA), the only known enzyme that cleaves the side chain of heparan sulfate, has been widely studied in relation to tumor metabolism, procoagulant activity, angiogenesis, inflammation and sepsis. It has been reported that HPA plays an important role in the progression of S-AKI. The aim of the present review was to provide an overview of the function of HPA in S-AKI and to summarize its underlying molecular mechanisms, including mediating inflammatory response, immune response, autophagy and exosome biogenesis. It is anticipated that emerging discoveries about HPA in S-AKI will support HPA as a potential biomarker and therapeutic target to combat S-AKI.

Contents

Correspondence to: Dr Li-Ping Liu, Department of Emergency, The First Hospital of Lanzhou University, 1 West Road, Donggang, Chengguan, Lanzhou, Gansu 730000, P.R. China
E-mail: liulipingldyy@126.com

Key words: sepsis, acute kidney injury, heparanase, exosomes, autophagy

1. Introduction

Sepsis-related acute kidney injury (S-AKI) is a severe complication of sepsis in critically ill patients, which is associated with a high morbidity and mortality rate and treatment cost (1,2). A previous meta-analysis showed that one in five adults and one in three children develop AKI during hospitalization globally (3), and a review reported that >50% of patients in intensive care units (ICUs) suffer from AKI (4). The mortality of patients with S-AKI is significantly higher than that of patients with AKI without sepsis (5). It is estimated that >60% of patients with sepsis or septic shock will develop S-AKI (5). Even if patients with S-AKI survive the acute phase, the prevalence of chronic kidney disease in these patients increases. Consequently, S-AKI is a major global challenge to the human population (6).

The main therapy for S-AKI is antibiotics combined with symptomatic treatment. When the complications cannot be treated by drug therapy alone, renal replacement therapy should be performed. Notably, there is still a lack of effective new drugs. Unfortunately, the precise pathogenetic mechanism underlying S-AKI is unclear; therefore, exploring the pathophysiology of S-AKI may provide novel options for its diagnosis and treatment. Previous studies have reported that heparanase (HPA) plays an important role in the pathogenesis of S-AKI (7,8).

2. S-AKI and its underlying molecular mechanisms

S-AKI is a syndrome that meets the Kidney Disease Improving Global Outcomes' criteria in patients with sepsis (9,10). In the criteria, AKI is defined as any of the following: Increase in serum creatinine (SCr) by 0.3 mg/dl (26.5 μmol/l) within 48 h; or increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/hour for 6 h. Previous studies have reported that the pathogenesis of S-AKI may be attributed to renal ischemia, hypoxia, toxic injury and sepsis in the clinic (11,12). In addition, an epidemiological study showed that the occurrence of S-AKI is associated with decreased renal perfusion and subsequent tubular necrosis (13). Furthermore, certain researchers have proposed alternative mechanisms for the pathogenesis of S-AKI. In a sheep model of *Escherichia coli*-induced septic shock, Maiden *et al* (14) showed that early AKI was not related to changes in renal

blood flow, oxygen delivery or histological appearance, such as glomerular mesangial expansion or podocyte disappearance. Lerolle *et al* (15) found that the renal damage caused by septic shock was not only a simple acute tubular injury, but was also associated with capillary leukocyte infiltration and apoptosis. Currently, microvascular dysfunction, inflammatory response and metabolic reprogramming are considered the three basic molecular mechanisms of S-AKI (16-18).

Microvascular dysfunction is characterized by an increased number of capillaries, cessation of blood flow and an uneven distribution of microvascular blood flow; it is considered the main cause of the pathophysiology of sepsis (19). Microvessels are the primary site for gas, nutrient and waste product exchange between blood and tissues. Sepsis leads to the dysfunction of the main cell types and fragments in microvessels, including endothelial cells (ECs), smooth muscle cells, red blood cells, white blood cells and platelets (20,21). ECs are vascular and non-traditional immune cells that play a major role in the systemic response to bacterial infection. Sepsis causes a series of impairments in ECs, leading to the dysregulation of microcirculation, leukocyte adhesion and migration, vasodilation, impaired transport of nutrients and increased capillary permeability, amongst other effects (22). During sepsis, hypoxia weakens the regulatory effects of red blood cells on microvascular relaxation and the deformability of red blood cells, causing the aggregation of red blood cells and ECs, and impairing microcirculatory blood flow (19,23). It has been reported that inducible nitric oxide synthase (iNOS) is heterogeneously expressed in different organic vascular beds, leading to pathological shunting of microvascular blood flow (24). Therefore, the increased activity of iNOS and the subsequent increase in the levels of NO may cause kidney (i.e., mitochondria and renal tubule) damage in septic shock (24,25). Furthermore, degradation of the endothelial glycocalyx, which is a major component of the vascular barrier, and plays an important role in microvascular homeostasis and organ perfusion, causes vascular leak, which also contributes to the occurrence of S-AKI (26). Thus, it may be inferred that sepsis causes microvascular dysfunction in AKI, including impairments of the main cell types in microvessels and the endothelial glycocalyx. As a result, the impairment of nutrient transport, leukocyte adhesion and migration, vasodilation and increased capillary permeability appear to be responsible for S-AKI.

An inflammatory response is the main defense mechanism of a host against pathogenic invasion. According to the Third International Consensus Definitions for Sepsis and Septic Shock (10), an imbalanced inflammatory response in the host may be the cause of organ dysfunction and adverse outcomes. Sepsis can induce the release of inflammatory mediators, such as pathogens and injury-related molecular patterns, into the intravascular lumen. These molecules bind to pattern recognition receptors, such as T-lymphoid receptors on the surface of immune cells, and initiate downstream cascade signals, leading to the synthesis and release of pro-inflammatory molecules (16). The dysregulated inflammatory response during sepsis can promote the release of cytokines and chemokines, commence leukocyte/platelet activation, increase the production of oxygen free radicals and arachidonic acid metabolites, and activate and recruit T cells, neutrophils, macrophages, platelets and ECs (27). Studies have shown that Toll-like receptors (TLRs) also play an important role in S-AKI (28,29). TLRs are the main pattern recognition receptors and can mediate cellular signaling cascades through a variety of pathogen-associated molecular patterns (PAMPs) (30,31). TLRs play a central role in the innate immune initiation process against invasive microbial pathogens. Renal tubular epithelial cells (TECs) also express TLRs, especially TLR2 and TLR4. Leemans *et al* (32) demonstrated that TLR2 expressed in the renal parenchyma plays a vital role in inducing inflammation and injury. The expression of the TLR4/NF-κB signaling pathway is enhanced in renal ischemia-reperfusion (I/R) injury and septic kidney injury (28). Another study showed that TLR4 expression in renal TECs regulates S-AKI and inflammation (33).

Currently, increasing attention is being paid to the interaction between inflammation, immunological mechanisms and coagulation cascades in triggering adaptive immune responses in renal TECs. These interactions amplify and enhance microvascular dysfunction and endothelial injury (34). During sepsis, the expression of adhesion molecules on ECs and immune cells is increased, resulting in decreased EC deformability, and increased ability to aggregate and activate neutrophils (22). During S-AKI, ECs, red blood cells, monocytes and platelets produce microvesicles (MVs), and endothelial microvascular damage may lead to increased concentrations of MVs (35). When the kidney is exposed to damage, PAMPs filter through glomeruli or adjacent peritubular capillaries, and proximal renal TECs exhibit increased oxidative stress, reactive oxygen species production and mitochondrial damage (16). In systemic infection and subsequent sepsis, dysregulation of immune thrombosis leads to systemic coagulopathy and multiorgan failure, due to microvascular obstruction depriving tissues of a blood supply. The main cellular drivers of this process are platelets and innate immune cells, such as neutrophils, eosinophils and macrophages (36). The activating interactions between platelets and immune cells is composed of coagulation and complement systems, which cause a coagulation cascade, leading to thrombosis and microcirculation dysfunction. Uncontrolled inflammation, activation of coagulation and complement cascades are considered to be involved in the pathogenesis of S-AKI (37). Metabolic reprogramming in response to injury is an evolutionarily conserved mechanism for cell survival (38). Cells convert nutrients to ATP through two key metabolic pathways: Oxidative phosphorylation (OXPHOS) and glycolysis. OXPHOS is the metabolic phenotype of TECs. The ability of OXPHOS to synthesize ATP depends on functional mitochondria (39). Sepsis is known to cause severe mitochondrial damage that may hinder the ability of TECs to restore OXPHOS. Persistence of glycolytic metabolism in renal TECs is associated with persistent local inflammation and increased injury. During sepsis, glycolysis may shift the TECs into 'off' mode, thus allowing the cell to re-prioritize energy expenditure for survival at the expense of organ function (38). As a result, renal tubular ion transport is reduced, resulting in an increase in chloride concentration in the renal tubular fluid. This decreases the glomerular filtration rate by activating tubuloglomerular feedback and causes AKI. An analysis of renal biopsies obtained 8 h after the induction of sepsis by cecal ligation and puncture (CLP) suggested a shift in the renal metabolic phenotype to glycolysis (40).

Although the mechanisms of S-AKI are widely studied, it is still necessary to explore the complex mechanisms of S-AKI pathogenesis to identify biomarkers and therapeutic targets. Previous studies have shown that HPA plays an important role in the S-AKI process (7,41).

3. Role of HPA in the pathogenesis of S-AKI

HPA is an endoglycosidase. HPA is also named HPA-1, which differs from HPA-2. The HPA gene, located on chromosome 4q21.2, is the sole known mammalian endoglycosidase that cleaves the heparan sulfate (HS) side chains of HS proteoglycans (HSPGs) intra- and extracellularly. *In vivo*, HPA exists within lysosomes as a precursor with a molecular weight of 65 kDa (42). The active form of HPA is generated by lysosomal cathepsin-induced cleavage of the pro-enzyme yielding 50- and 8-kDa fragments, both of which are needed for its activity. Active HPA has enzymatic and non-enzymatic activities that participate in multiple processes (42). HPA serves an important role in promoting pathological processes such as tumor growth, metastasis, angiogenesis, thrombosis, fibrosis, inflammation, autoimmunity and renal dysfunction (43-49). Upregulation of HPA expression is associated with tumor size and progression, enhanced metastasis and a poor prognosis (50).

When HPA is secreted outside the cell, it cleaves the HS side chain and contributes to the activation of integrin, epidermal growth factor receptor and other signaling pathways. HPA not only trims HS that is bound to glycocalyx proteoglycan core proteins, but also degrades proteoglycans that are attached to the extracellular matrix (ECM), thus remodeling the ECM. HS is a high-sulfur polysaccharide that is widely found in the ECM and plasma membrane, and within the cell (51). Therefore, it plays an important role in maintaining ECM integrity, barrier function and cell-ECM interactions (52). HPA is crucial for the normal turnover of HS (53). HPA affects the function of HSPGs by degrading HS. Several linear HS chains covalently bind to a core protein to form HSPGs, which participate in cell-cell and cell-matrix adhesion (54). HSPGs not only provide a repository for heparin-binding molecules, such as growth factors, chemokines and enzymes in the tissue microenvironment, but also regulate their accessibility, function and mode of action. Degradation of HS by HPA not only begins to remove physical barriers that prevent cell invasion, but also releases various proteins that bind to HS, promoting activation of cellular signaling pathways and responses (55). However, it has been reported that the exact role of HPA in inflammation is difficult to determine, as HPA may act in other ways, either enhancing or inhibiting the inflammatory response (47).

Intracellular HPA binds to autophagosomes to enable autophagy, binds to exosomes to promote their release from cells and enters the nucleus to regulate gene expression (56). In addition, HPA has an important role in the normal physiology of lysosomes (57). HPA regulates gene expression, activates innate immune cells, promotes the formation of exosomes and autophagosomes, and promotes signal transduction through enzymatic and non-enzymatic activities (58). HPA promotes the secretion of exosomes that interact with tumor and host cells, and drives their transition to an aggressive tumor phenotype (57). Exosomes are mediators of intercellular communication that initiate tumor progression by regulating tumor and host cell behavior locally and distally throughout the body in the tumor microenvironment (59). HPA enhances tumor growth and chemotherapy resistance by enhancing autophagy (60).

HPA affects S-AKI by degrading the endothelial glycocalyx. HPA promotes degradation of the endothelial glycocalyx in glomeruli and renal tubules during sepsis (Fig. 1). The glycocalyx covers the surface of the vascular endothelium and its degradation destroys the integrity and permeability of the vascular system. Lygizos *et al* (7) showed that glomerular HPA was activated during sepsis and contributed to the occurrence of S-AKI. HPA destroys the integrity and permeability of renal TECs by degrading HS, resulting in renal inflammation, and urinary HS primarily reflects the degradation of the renal glycocalyx (7). Schmidt *et al* (61) compared 30 patients with septic shock in the medical ICU with 25 patients with severe trauma in the surgical ICU that acted as controls. The study revealed that compared with that in the control group, the level of HS in the urine of septic patients was significantly higher. The degradation function of HPA on HS suggests that HPA may contribute to regulation of the renal glycocalyx during sepsis and lead to S-AKI.

HPA functions in I/R AKI and toxic AKI. HPA not only promotes the progression of S-AKI, but also plays an important role in other types of AKI, such as toxic AKI. I/R is a complication of AKI and HPA is part of the biological network triggered by I/R injury (62). Masola *et al* (62) demonstrated through *in vivo* and *in vitro* experiments that HPA can regulate macrophage polarization, and renal damage and repair following I/R, and that HPA inhibitors can partially restore renal function and reduce apoptosis. In addition, another study showed that HPA promotes the onset of I/R-induced AKI in an I/R mouse model (63). This previous study found that HPA is upregulated in I/R mouse models, particularly in HPA-overexpressing transgenic mice, whereas pretreatment with PG545, an HPA inhibitor, can eliminate I/R-induced renal dysfunction. Another study demonstrated that HPA is a key factor involved in the occurrence and development of I/R-induced epithelial-mesenchymal transition (EMT) (64). In a podocyte model of Adriamycin-induced toxic kidney injury, HPA overexpression was shown to preserve glomerular structure and renal function, and elevated HPA levels could promote cell protection against apoptosis (65), thus exhibiting a protective effect. This previous study also reported that exposure to toxic damage resulted in a significant increase in autophagic flux in the podocytes of HPA-overexpressing mice, which could be reversed by the HPA inhibitor, Roneparstat.

Therefore, previous studies have suggested that HPA plays an important role in pathological processes, such as tumor growth, migration/invasion of ECs, infiltration of immune cells, metastasis, angiogenesis, thrombosis, fibrosis, autoimmunity, autophagy, exosome release, promotion of pro-inflammatory cell adhesion, signal transduction and renal dysfunction (42-44,46,57,66-71).

HPA mediates its effects on S-AKI through inflammatory and immune responses. HPA plays an important role in inflammation, sepsis and AKI (72-74). Furthermore, HPA has effects on the endothelial glycocalyx and ECM in the kidney. HPA

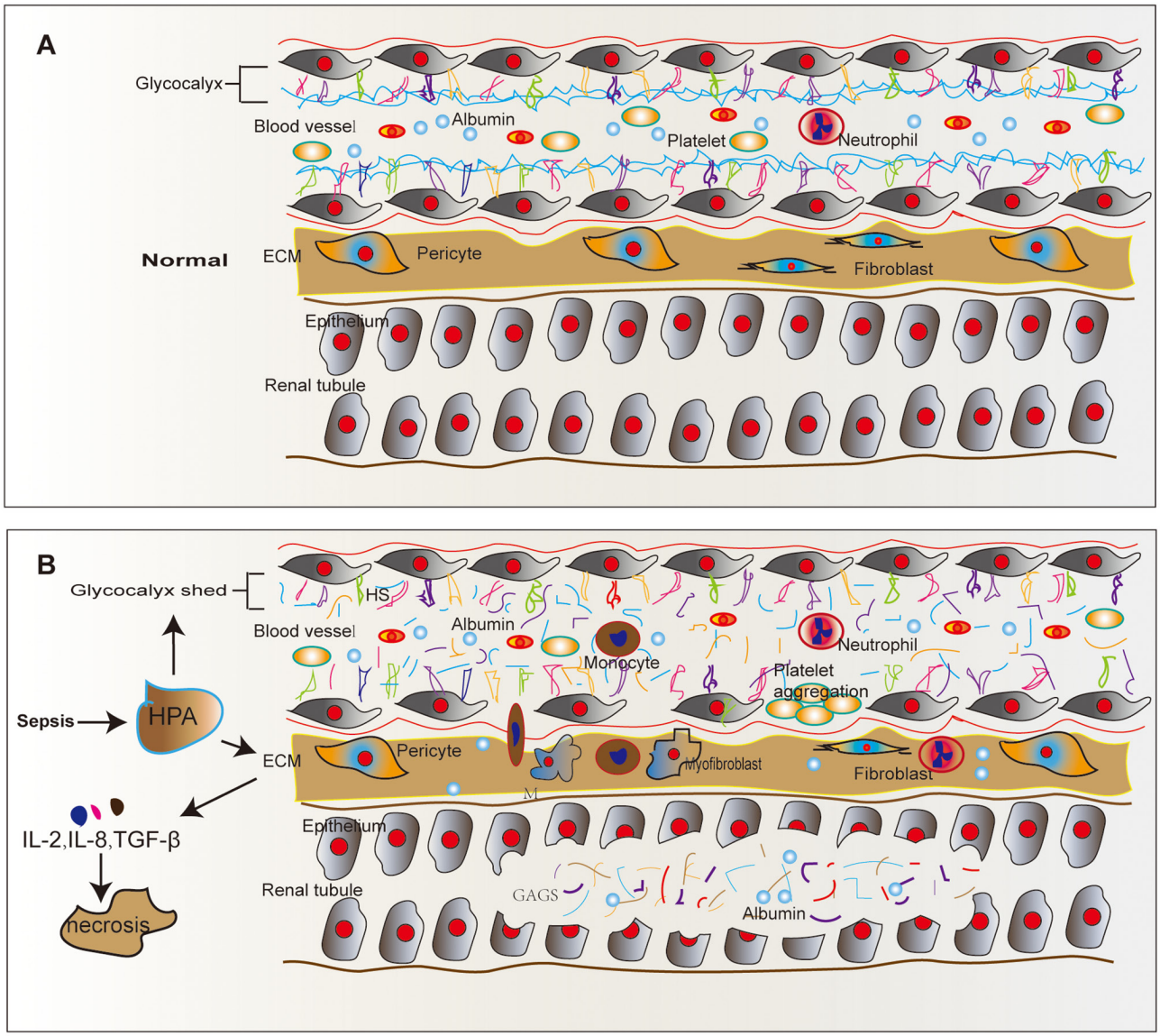

Figure 1. Structure of renal tubular epithelial cells in normal and septic conditions. (A) Normal renal tubular epithelial cells. (B) HPA acts on renal tubular epithelial cells during sepsis. HPA engages in glycocalyx degradation in sepsis. HPA also functions on ECM, causing the release of its pro-inflammatory factors, such as IL-2, IL-8, bFGF and TGF-β, and stimulating leukocyte recruitment, migration and extravasation by regulating the interaction between leukocytes and endothelial cell surface. ECM, extracellular matrix; HS, heparan sulfate; HPA, heparanase; GAGs, glycosaminoglycans; M, monocyte.

is activated under inflammatory conditions and can promote the degradation and shedding of the glycocalyx, leading to increased cell permeability, thus causing vascular leakage and hypovolemia. HPA also mediates its enzymatic activity on the ECM, particularly the basement membrane, and promotes the release of pro-inflammatory factors (i.e., IL-2, IL-8, basic fibroblast growth factor and TGF-β) and heparin-binding molecules in the ECM. These inflammatory factors stimulate the recruitment, rolling process and extravasation of leukocytes by regulating the interaction between leukocytes and the ECM surface (75-77) (Fig. 1).

There is additional evidence to support the role of HPA in S-AKI through the immune response during sepsis. In S-AKI, HPA increases the presence of adhesion molecules, and enhances vascular permeability, tissue edema, leukocyte adhesion, platelet aggregation and vasodilation-related dysfunction by promoting glycocalyx degradation (78,79). The glycocalyx plays a vital role in maintaining the integrity and permeability of the vascular system, providing vascular tension and regulating leukocyte adhesion (80). HPA induces the apoptosis of tubular cells and induces the production of damage-associated molecular patterns. HS fragments released by HPA can also activate TLRs on macrophages and tubular cells (62). Tubular cells produce proinflammatory cytokines in response to direct hypoxic stimulation and TLR activation, resulting in the attraction and activation of macrophages. In addition, high levels of HPA can promote M1 polarization of infiltrating macrophages and aggravate parenchymal injury (62). HPA also induces a procoagulant effect and renal fibrosis by binding to cellular HS (48), and interacts with tissue factor pathway inhibitor (TFPI) on the surface of ECs, resulting in TFPI dissociation and cell coagulation activity promotion (81). In addition, during S-AKI, HPA leads to platelet aggregation and vasodilation-related dysfunction by promoting glycocalyx

degradation. Furthermore, it can lead to increased microvascular dysfunction and endothelial injury, thus affecting microcirculatory blood flow and aggravating coagulation (74). HPA is also involved in hemostasis through non-enzymatic mechanisms (48). For example, HPA reduces unfractionated heparin to low-molecular weight heparin, which functions as a co-factor for factor Xa inhibition by antithrombase (48). Bayam *et al* (82) confirmed that elevated heparin levels may promote thrombosis. Therefore, HPA may also enhance procoagulant activity in S-AKI. In addition, HPA can promote renal fibrosis. Abassi *et al* (63) confirmed that PG545 suppressed renal dysfunction and the upregulation of HPA, as well as pro-inflammatory and pro-fibrotic factors that were induced by I/R in AKI. HPA promotes renal fibrosis by participating in fibroblast growth factor-2-dependent EMT of renal TECs (83).

In conclusion, HPA plays a major role in S-AKI, mainly through the degradation of the endothelial glycocalyx, the remodeling of the ECM, and the release of pro-inflammatory cytokines and heparin-binding molecules in the ECM, thus aggravating the immune response and inducing a procoagulant effect and renal fibrosis. However, HPA may also influence S-AKI through other mechanisms.

HPA mediates its effects on S-AKI through autophagy. Autophagy is a highly conserved lysosome degradation pathway in mammals, which removes protein aggregates and damaged organelles to maintain cellular homeostasis (84,85). It is reported that autophagy occurs at low levels under physiological conditions to maintain the homeostasis of the intracellular environment, but is upregulated upon exposure to stress conditions, such as hunger, hypoxia, ischemia and oxidative stress (86). In healthy and diseased states, autophagy plays a key role in maintaining the morphology, activity and dynamic balance between various cell types in the kidney (87). It has been reported that autophagy induced by unilateral ureteral obstruction (UUO) has renoprotective effects, and treatment with the autophagy inhibitor, 3-methyladenine, enhances tubular cell apoptosis and tubulointerstitial fibrosis in the obstructed kidney following UUO (88). However, uncontrolled autophagy leads to excessive degradation of cellular proteins and organelles, eventually resulting in the death of autophagic cells (89).

A previous study has shown that HPA regulates autophagy (90). Shteingauz *et al* (60) and White (91) first described the role of lysosomal HPA in regulating autophagy, which presents intracellular proteins, lipids and other molecules or organelles for degradation and recycling. The PI3K/AKT/mTOR signaling pathway is known to inhibit autophagy (92). Certain studies (60,93) have reported that overexpression of HPA downregulates mTOR activity, and the inhibition of HPA by PG545 reverses this. mTOR is usually scattered throughout the cytoplasm of normal cells; however, when HPA expression increases, the majority of mTOR and HPA is concentrated around the nucleus, thus reducing the activity of mTOR and increasing autophagy (94). Therefore, it was speculated that HPA may cause renal autophagy through the PI3K/Akt/mTOR signaling pathway and promote the progression of S-AKI (Table I; the protective role in S-AKI). HPA may also cause renal autophagy through the AMPK/mTOR signaling pathway, which is another autophagy signaling pathway. Further in-depth investigations are needed to validate these hypotheses.

HPA mediates its action through exosomes during S-AKI. Exosomes are membranous vesicles with a diameter of 40-100 mm. All living cells secrete exosomes, which exist in the blood, urine, saliva, lymph and other body fluids (95,96). Exosomes do not contain nuclei and cannot self-replicate. Exosomes are, reportedly, relatively good drug delivery systems due to their stability. Recipient cells endocytose exosomes and release exosome contents, and thus play a crucial role in cell-to-cell communication and information transmission, as exosomes are involved in transporting proteins, lipids, microRNA (miRNA/miR), mRNA and other bioactive substances. Exosomes also participate in the regulation of the inflammatory response, immune response, tumorigenesis, infection and other pathophysiological processes (97,98). Additionally, exosomes have a significant role in sepsis. The overall contribution of exosomes to sepsis was previously studied using GW4869, which was shown to inhibit the production of exosomes. Essandoh *et al* (99) showed that GW4869 significantly improved the survival rate of mice injected with lipopolysaccharide (LPS) or the septic mouse model of CLP.

Exosomes affect S-AKI by carrying relevant cargo, such as miRNAs. miRNAs are released into body fluids, such as serum and urine, and their high specificity and sensitivity render them suitable for use as potential biomarkers for monitoring the progression of AKI (100). Viñas *et al* (101) reported that the levels of miR-486-5p expressed in the proximal tubules and ECs were increased upon injection with miR-486-5p mimics into AKI mice. Furthermore, the levels of plasma creatinine, tissue damage, and neutrophil infiltration and apoptosis improved. Urinary exosomes are excreted by all nephron segments. Exosome miR-27b from bone marrow mesenchymal stem cells has been shown to inhibit the development of sepsis by downregulating Jumonji domain-containing protein-3 and inactivating the NF-κB signaling pathway (102). Zhang *et al* (103) showed that human umbilical cord mesenchymal stem cell-derived exosomes downregulated the expression of the miR-146b target gene, interleukin-1 receptor-associated kinase, by upregulating the expression of miR-146b. Furthermore, a previous study showed that exosome-mediated pyroptosis of miR-93-TXNIP-NLRP3 creates functional differences between M1 and M2 macrophages in S-AKI (104). miR-19b-3p, derived from LPS-induced AKI mouse TECs, has been reported to promote macrophage infiltration and tubulointerstitial inflammation by inhibiting the suppressor of cytokine signaling-1 *in vitro*, leading to the activation of NF-κB, and upregulation of monocyte chemoattractant protein-1 (MCP-1), IL-1β, IL-6, TNF-α and iNOS (105) (Fig. 2).

HPA promotes the formation of exosomes. HPA-induced enhancement of exosome biogenesis was initially identified in human myeloma cells transfected with HPA cDNA (106). The formation of extracellular vesicles is dependent on syntenin and its interaction with syndecans. Roucourt *et al* (107) reported that HPA activated the syndecan-syntenin-ALIX exosome pathway, and that it also played a role in regulating this pathway. Syndecans, a family of membrane proteoglycans, are composed of chondroitin sulfate and HS chains linked to a 31-kDa integral membrane protein (108). Syndecans and syntenin are involved in the regulation of exosome biogenesis

Table I. Role of heparanase in sepsis-related acute kidney injury.

A, Adverse role

Activity	Action	Area	Outcomes	(Refs.)
Enzymatic activity	Degrade HS side chain	Glomerular ECs and glomerular basement membrane	Damage to glomerular filtration barrier; proteinuria; renal insufficiency	(62,69)
		Renal interstitial vascular ECs	Renal interstitial inflammatory infiltration	(34)
		Renal TECs	Destruction of integrity and permeability; enhancement of renal inflammation	(69)
		Glycocalyx	Enhancement of vascular permeability, tissue edema, leukocyte adhesion and platelet aggregation; vasodilation disorder	(78-80)
		ECM	Destruction of ECM integrity and barrier function; release of its pro-inflammatory factors; stimulation of leukocyte recruitment, rolling process and extravasation	(52,75-78)
Non-enzymatic activity	Procoag ulant activity	Extracellular	Promotion of thrombosis	(82)
	Bind to autopha gosome	Intracellular	Promotion of autophagy to break the cellular homeostasis	(60,91,92)
	Bind to exosome	Intracellular	Entering of the nucleus to affect gene transcription	(58,108)

B, Protective role

Activity	Action	Area	Outcomes	(Refs.)
Non-enzymatic activity	Bind to autopha gosome	Intracellular	Promotion of autophagy to maintain cellular homeostasis	(89,90)
	Bind to exosome	Intracellular	Entering of the nucleus to affect gene transcription through the substances carried by exosomes	(58)
	Procoag ulant activity	Extracellular	Involvement in hemostasis and relieve bleeding	(48)

HS, heparan sulfate; ECs, endothelial cells; TECs, tubular ECs; ECM, extracellular matrix.

through their interaction with ALIX (109). However, HPA alters syndecan and syntenin composition, and biological function through promoting exosome secretion (106). In human cancer cells, exosome secretion is significantly increased when HPA expression is enhanced or when tumor cells are exposed to exogenous HPA. Furthermore, HPA activity is necessary to enhance exosome secretion (106). In conclusion, HPA is involved in exosome biogenesis and activates the syndecan-syntenin-ALIX pathway (Fig. 2).

HPA mediates its action through exosomes during S-AKI. HPA promotes exosome formation, which act on the kidneys through their biologically relevant cargo. It has been reported that the upregulation of miR-21-5p improves renal function through several mechanisms; it has been shown to reduce the pathological damage to renal tissue, reduce serum inflammatory response, reduce renal tissue apoptosis, reduce oxidative stress responses and regulate the expression of endothelial glycocalyx injury markers, such as syndecan-1 and HPA in CLP rats (8). HPA also enters the nucleus and regulates gene transcription through exosomes. The role of HPA in exosome activity has been determined by its regulation of HS cleavage (55). HPA localizes to the exosome surface, where it is activated and degrades HS within the ECM (110). HPA can regulate the transcription of various genes involved in neovascularization, such as matrix metalloproteinase 9 (MMP-9), coagulation and inflammatory responses. HPA has been shown to increase the expression of MMP-9 and to increase cleavage of syndecan-1. The released syndecan-1 can be transported into the nucleus, where the bound HS chain and HPA

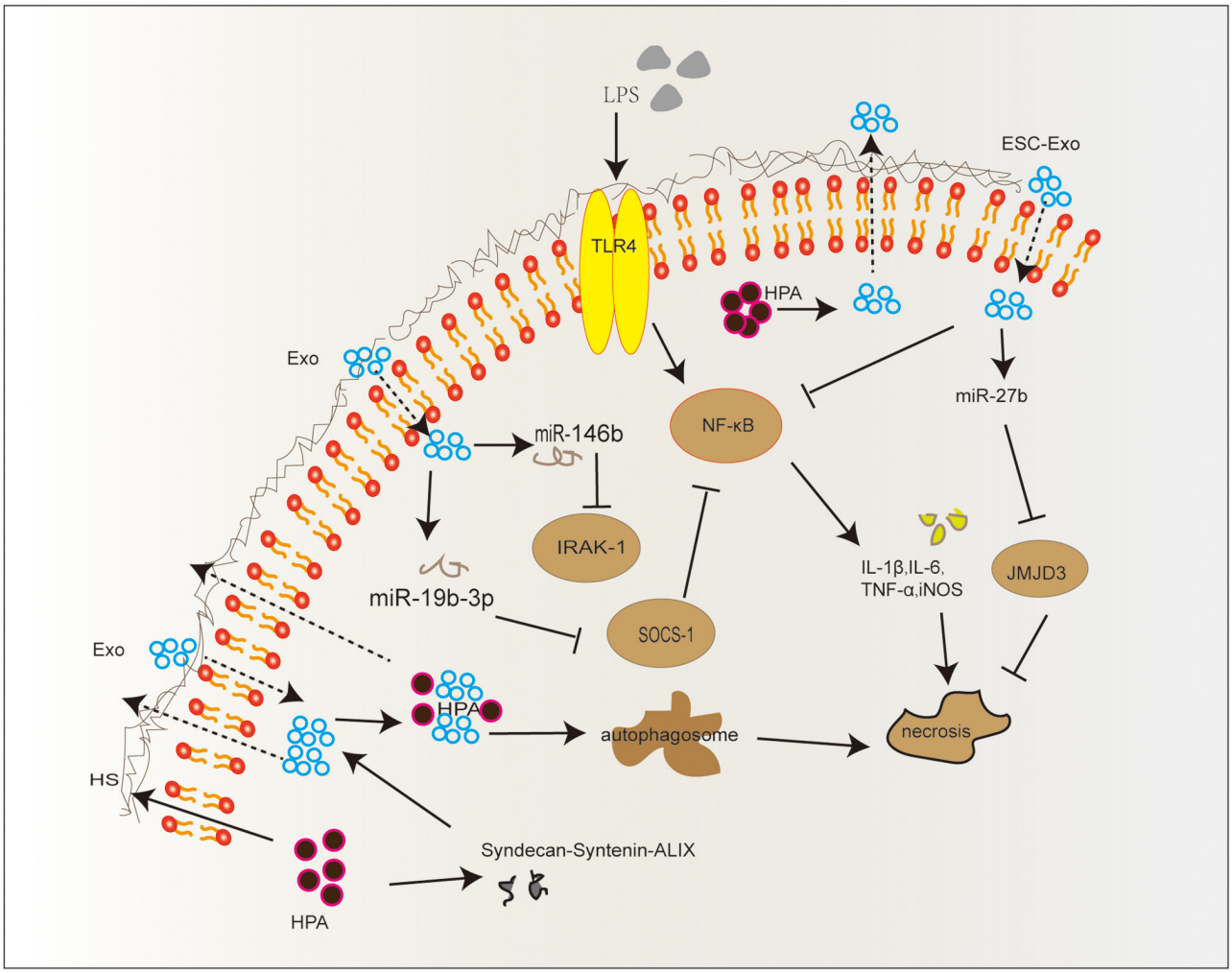

Figure 2. HPA activates the syndecan-syntenin-ALIX exosome pathway. Exo, exosomes; HS, heparan sulfate; HPA, heparanase; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; ESC-Exo, mesenchymal stem cell-derived exosomes; SOCS-1, suppressor of cytokine signaling-1; JMJD3, Jumonji domain containing 3; iNOS, inducible nitric oxide synthase; IRAK-1, interleukin-1 receptor associated kinase 1; miR, microRNA.

transported into the nucleus can affect a number of mechanisms, including promotion of mitotic spindle formation and subsequent chromosome stability, inhibition of DNA topoisomerase I activity and regulation of cell proliferation (55). In conclusion, HPA functions on S-AKI through exosomes and the release of bioactive substances, and certain miRNAs derived from exosomes can improve renal function in S-AKI (Table I; the protective roles of HPA in S-AKI).

In conclusion, HPA contributes to the pathogenesis of S-AKI by inducing the degradation of HS and the destruction of ECM, thus promoting inflammation, macrophage polarization, fibrosis, dysregulation of inflammatory response, excessive activation of autophagy and exosome biogenesis (Table I, the adverse roles of HPA in S-AKI.). However, the precise molecular mechanisms underlying the pathogenesis of S-AKI require further investigation.

4. HPA as a diagnostic biomarker and therapeutic target for S-AKI

Currently, several molecules have been identified as potential biomarkers for the early detection of renal damage prior to increased serum creatinine levels (4). For example, tissue inhibitor of metalloproteinase 2, insulin-like growth factor binding protein 7, liver fatty acid binding protein, neutrophil gelatinase-associated lipocalin and cystatin C (111-114), amongst others, have been reported as potential biomarkers for renal damage. However, due to their limited specificity and sensitivity, injury markers are mainly only used for research purposes at this time (4). Notably, in a septic model of CLP, the level of HPA was moderately increased at 4 h and further increased after 24 h (115). HPA is activated in AKI and plays a key role in endothelial glycan shedding (74,116). HPA may also serve as a potential biomarker for S-AKI. In a CLP-induced mouse model of S-AKI, renal function was damaged after 4 h (7). The study showed that CLP-treated mice exhibited early activation of glomerular HPA and loss of glomerular filtration, as indicated by a greater than two-fold increase in blood urea nitrogen and a >50% decrease in inulin clearance. However, administration of HPA inhibitors 2 h prior to CLP was revealed to attenuate sepsis-induced glomerular filtration rate loss.

The inhibition of HPA activity alleviates the degradation of HS, thereby protecting the glycocalyx and preserving the vascular barrier. HPA inhibitors, such as PG545, PI-88, SST0001, other HS analogues and heparin-derived drugs, have

been reported to inhibit the activity of HPA during inflammation (42). Endothelial progenitor cell-derived exosomes were reported to increase the level of syndecan-1 and decrease the level of HPA in the renal tissues of CLP rats (8). *In vivo*, phillyrin, the main pharmacological component of the traditional Chinese medicine *Forsythia suspensa*, has an effective protective effect on glycocalyx HS degradation in LPS-induced AKI mice (41).

Based on the effects of HPA in S-AKI, it is expected to serve as a novel biomarker for the detection and treatment of S-AKI. However, HPA inhibitors have not yet been tested in the clinic. The identification of a specific, safe and efficacious HPA inhibitor may pave the way for its application in the clinic for the treatment of patients with S-AKI, perhaps reducing the mortality rate.

5. Limitations

HPA-2 is a protein located on chromosome 10q23-24. HPA-2 has 40% sequence homology with the coding region of another protein, HPA-1, but despite this, they have different functions and effects (117). The total length of HPA-2 is 592 amino acids, with the two proteins, HPA-2 and HPA-1, sharing 47% of their amino acids. HPA-2 can bind to HS, but has no enzymatic activity and lacks the ability to degrade HS (118). Despite its lack of endoglycosidase activity, HPA-2 has a higher affinity for HS than HPA-1; therefore, by competing for HS, it inhibits the enzymatic activity of HPA-1 (119). HPA-2 plays an important role in embryonic development, but its mechanisms and biological functions remain unclear. HPA-2 appears to be upregulated in benign and less aggressive tumors, and may function as a tumor suppressor (118). At present, there are no studies on the association between HPA-2, sepsis and S-AKI. Therefore, the HPA mentioned in this review only refers to HPA-1 without much focus on HPA-2.

6. Summary and future perspectives

HPA plays a major role in the pathogenesis of S-AKI, but the precise molecular mechanism requires further exploration. HPA may serve as a potential biomarker for the early diagnosis and treatment of S-AKI. HPA mediates its action through exosomes in S-AKI, which may transport potential biomarkers of S-AKI. Therefore, such biomarkers could potentially offer a novel approach to the diagnosis of S-AKI.

Early intervention with targeted therapy for patients with S-AKI may improve their prognosis. HPA inhibitors, exosomes and autophagy regulators could serve as potential therapeutic strategies for S-AKI. Further studies exploring the crosstalk between HPA, autophagy and exosomes are required to determine the underlying molecular mechanisms.

Acknowledgements

Not applicable.

Funding

The present study was funded by the Science and Technology Department of Gansu (grant no. 20JR5RA35), the Talent Innovation and Entrepreneurship Project of Science and Technology Bureau of Chengguan, Lanzhou (grant no. 2020RCCX0030), the Lanzhou Science and Technology Development Guiding Plan Project (grant no. 2019-ZD-37), the Fund of The First Hospital of Lanzhou University (grant no. Ldyyyn2018-48), The Open Topics of the Key Laboratory of Biological Treatment and Regenerative Medicine in Gansu (grant no. zdsyskfkt-201702), and the Science and Technology Program of Gansu (grant no. 21JR7RA418).

Availability of data and materials

Not applicable.

Authors' contributions

LPL proposed the current study and was responsible for its design and review. JCL designed and wrote the manuscript. LJW analyzed the feasibility of the manuscript, researched the literature and was responsible for reviewing the manuscript. FF and TTC researched and reviewed the literature and the manuscript. WGS corrected and revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, Liu KD, Mehta RL, Pannu N, Van Biesen W and Vanholder R.: Acute kidney injury: An increasing global concern. Lancet 382: 170-179, 2013.
2. Hoste EA and Schurgers M: Epidemiology of acute kidney injury: How big is the problem? Crit Care Med 36 (4 Suppl): S146-S151, 2008.
3. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F, Koulouridis I and Jaber BL; Acute Kidney Injury Advisory Group of the American Society of Nephrology: World incidence of AKI: A meta-analysis. Clin J Am Soc Nephrol 8: 1482-1493, 2013.
4. Ronco C, Bellomo R and Kellum JA: Acute kidney injury. Lancet 394: 1949-1964, 2019.
5. Kellum JA, Chawla LS, Keener C, Singbartl K, Palevsky PM, Pike FL, Yealy DM, Huang DT and Angus DC; ProCESS and ProGReSS-AKI Investigators: The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. Am J Respir Crit Care Med 193: 281-287, 2016.
6. Mayeux PR and MacMillan-Crow LA: Pharmacological targets in the renal peritubular microenvironment: Implications for therapy for sepsis-induced acute kidney injury. Pharmacol Ther 134: 139-155, 2012.
7. Lygizos MI, Yang Y, Altmann CJ, Okamura K, Hernando AA, Perez MJ, Smith LP, Koyanagi DE, Gandjeva A, Bhargava R, *et al*: Heparanase mediates renal dysfunction during early sepsis in mice. Physiol Rep 1: e00153, 2013.

8. Zhang Y, Huang H, Liu W, Liu S, Wang XY, Diao ZL, Zhang AH, Guo W, Han X, Dong X and Katilov O: Endothelial progenitor cells-derived exosomal microRNA-21-5p alleviates sepsis-induced acute kidney injury by inhibiting RUNX1 expression. Cell Death Dis 12: 335, 2021.
9. Kellum JA and Lameire N; KDIGO AKI Guideline Work Group: Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (Part 1). Crit Care 17: 204, 2013.
10. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, *et al*: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315: 801-810, 2016.
11. Bonventre JV and Yang L: Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest 121: 4210-4221, 2011.
12. Schrier RW, Wang W, Poole B and Mitra A: Acute renal failure: Definitions, diagnosis, pathogenesis, and therapy. J Clin Invest 114: 5-14, 2004.
13. Schmidt C, Steinke T, Moritz S, Graf BM and Bucher M: Acute renal failure and sepsis: Just an organ dysfunction due to septic multiorgan failure? Anaesthesist 59: 682-699, 2010 (In German).
14. Maiden MJ, Otto S, Brealey JK, Finnis ME, Chapman MJ, Kuchel TR, Nash CH, Edwards J and Bellomo R: Structure and function of the kidney in septic shock. A prospective controlled experimental study. Am J Respir Crit Care Med 194: 692-700, 2016.
15. Lerolle N, Nochy D, Guérot E, Bruneval P, Fagon JY, Diehl JL and Hill G: Histopathology of septic shock induced acute kidney injury: Apoptosis and leukocytic infiltration. Intensive Care Med 36: 471-478, 2010.
16. Peerapornratana S, Manrique-Caballero CL, Gómez H and Kellum JA: Acute kidney injury from sepsis: Current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Int 96: 1083-1099, 2019.
17. Poston JT and Koyner JL: Sepsis associated acute kidney injury. BMJ 364: k4891, 2019.
18. Gomez H, Ince C, De Backer D, Pickkers P, Payen D, Hotchkiss J and Kellum JA: A unified theory of sepsis-induced acute kidney injury: Inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. Shock 41: 3-11, 2014.
19. Bateman RM, Sharpe MD, Jagger JE and Ellis CG: Sepsis impairs microvascular autoregulation and delays capillary response within hypoxic capillaries. Crit Care 19: 389, 2015.
20. Ye C, Kawasaki M, Nakano K, Ohnishi T, Watanabe E, Oda S, Nakada TA and Haneishi H: Acquisition and analysis of microcirculation image in septic model rats. Sensors (Basel) 22: 8471, 2022.
21. Ince C: The microcirculation is the motor of sepsis. Crit Care 9 (Suppl 4): S13-S19, 2005.
22. Joffre J, Hellman J, Ince C and Ait-Oufella H: Endothelial responses in sepsis. Am J Respir Crit Care Med 202: 361-370, 2020.
23. Anniss AM and Sparrow RL: Variable adhesion of different red blood cell products to activated vascular endothelium under flow conditions. Am J Hematol 82: 439-445, 2007.
24. Ishikawa K, Calzavacca P, Bellomo R, Bailey M and May CN: Effect of selective inhibition of renal inducible nitric oxide synthase on renal blood flow and function in experimental hyperdynamic sepsis. Crit Care Med 40: 2368-2375, 2012.
25. Heemskerk S, Pickkers P, Bouw MP, Draisma A, van der Hoeven JG, Peters WH, Smits P, Russel FG and Masereeuw R: Upregulation of renal inducible nitric oxide synthase during human endotoxemia and sepsis is associated with proximal tubule injury. Clin J Am Soc Nephrol 1: 853-862, 2006.
26. Inkinen N, Pettilä V, Lakkisto P, Kuitunen A, Jukarainen S, Bendel S, Inkinen O, Ala-Kokko T and Vaara ST; FINNAKI Study Group: Association of endothelial and glycocalyx injury biomarkers with fluid administration, development of acute kidney injury, and 90-day mortality: Data from the FINNAKI observational study. Ann Intensive Care 9: 103, 2019.
27. Gustot T: Multiple organ failure in sepsis: Prognosis and role of systemic inflammatory response. Curr Opin Crit Care 17: 153-159, 2011.
28. Zhu J, Zhang Y, Shi L, Xia Y, Zha H, Li H and Song Z: RP105 protects against ischemic and septic acute kidney injury via suppressing TLR4/NF-κB signaling pathways. Int Immunopharmacol 109: 108904, 2022.
29. Krivan S, Kapelouzou A, Vagios S, Tsilimigras DI, Katsimpoulas M, Moris D, Aravanis CV, Demesticha TD, Schizas D, Mavroidis M, *et al*: Increased expression of Toll-like receptors 2, 3, 4 and 7 mRNA in the kidney and intestine of a septic mouse model. Sci Rep 9: 4010, 2019.
30. Kawai T and Akira S: Signaling to NF-kappaB by Toll-like receptors. Trends Mol Med 13: 460-469, 2007.
31. Kawai T and Akira S: TLR signaling. Semin Immunol 19: 24-32, 2007.
32. Leemans JC, Stokman G, Claessen N, Rouschop KM, Teske GJ, Kirschning CJ, Akira S, van der Poll T, Weening JJ and Florquin S: Renal-associated TLR2 mediates ischemia/reperfusion injury in the kidney. J Clin Invest 115: 2894-2903, 2005.
33. El-Achkar TM, Huang X, Plotkin Z, Sandoval RM, Rhodes GJ and Dagher PC: Sepsis induces changes in the expression and distribution of Toll-like receptor 4 in the rat kidney. Am J Physiol Renal Physiol 290: F1034-F1043, 2006.
34. Fani F, Regolisti G, Delsante M, Cantaluppi V, Castellano G, Gesualdo L, Villa G and Fiaccadori E: Recent advances in the pathogenetic mechanisms of sepsis-associated acute kidney injury. J Nephrol 31: 351-359, 2018.
35. Zafrani L, Gerotziafas G, Byrnes C, Hu X, Perez J, Lévi C, Placier S, Letavernier E, Leelahavanichkul A, Haymann JP, *et al*: Calpastatin controls polymicrobial sepsis by limiting procoagulant microparticle release. Am J Respir Crit Care Med 185: 744-755, 2012.
36. Stark K and Massberg S: Interplay between inflammation and thrombosis in cardiovascular pathology. Nat Rev Cardiol 18: 666-682, 2021.
37. Benedetti C, Waldman M, Zaza G, Riella LV and Cravedi P: COVID-19 and the Kidneys: An update. Front Med (Lausanne) 7: 423, 2020.
38. Toro J, Manrique-Caballero CL and Gómez H: Metabolic reprogramming and host tolerance: A novel concept to understand sepsis-associated AKI. J Clin Med 10: 4184, 2021.
39. Wilson DF: Oxidative phosphorylation: Regulation and role in cellular and tissue metabolism. J Physiol 595: 7023-7038, 2017.
40. Waltz P, Carchman E, Gomez H and Zuckerbraun B: Sepsis results in an altered renal metabolic and osmolyte profile. J Surg Res 202: 8-12, 2016.
41. Zhang D, Qi B, Li D, Feng J, Huang X, Ma X, Huang L, Wang X and Liu X: Phillyrin relieves lipopolysaccharide-induced AKI by protecting against glycocalyx damage and inhibiting inflammatory responses. Inflammation 43: 540-551, 2020.
42. Vlodavsky I, Singh P, Boyango I, Gutter-Kapon L, Elkin M, Sanderson RD and Ilan N: Heparanase: From basic research to therapeutic applications in cancer and inflammation. Drug Resist Updat 29: 54-75, 2016.
43. Goldberg R, Meirovitz A, Hirshoren N, Bulvik R, Binder A, Rubinstein AM and Elkin M: Versatile role of heparanase in inflammation. Matrix Biol 32: 234-240, 2013.
44. Goldberg R, Rubinstein AM, Gil N, Hermano E, Li JP, van der Vlag J, Atzmon R, Meirovitz A and Elkin M: Role of heparanase-driven inflammatory cascade in pathogenesis of diabetic nephropathy. Diabetes 63: 4302-4313, 2014.
45. Goldshmidt O, Zcharia E, Abramovitch R, Metzger S, Aingorn H, Friedmann Y, Schirrmacher V, Mitrani E and Vlodavsky I: Cell surface expression and secretion of heparanase markedly promote tumor angiogenesis and metastasis. Proc Natl Acad Sci USA 99: 10031-10036, 2002.
46. Parish CR, Freeman C, Ziolkowski AF, He YQ, Sutcliffe EL, Zafar A, Rao S and Simeonovic CJ: Unexpected new roles for heparanase in type 1 diabetes and immune gene regulation. Matrix Biol 32: 228-233, 2013.
47. Meirovitz A, Goldberg R, Binder A, Rubinstein AM, Hermano E and Elkin M: Heparanase in inflammation and inflammation-associated cancer. FEBS J 280: 2307-2319, 2013.
48. Levey AS and James MT: Acute kidney injury. Ann Intern Med 167: ITC66-ITC80, 2017.
49. Masola V, Zaza G, Onisto M, Lupo A and Gambaro G: Impact of heparanase on renal fibrosis. J Transl Med 13: 181, 2015.
50. Rosenfeldt MT and Ryan KM: The multiple roles of autophagy in cancer. Carcinogenesis 32: 955-963, 2011.
51. Bishop JR, Schuksz M and Esko JD: Heparan sulphate proteoglycans fine-tune mammalian physiology. Nature 446: 1030-1037, 2007.
52. Bernfield M, Götte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J and Zako M: Functions of cell surface heparan sulfate proteoglycans. Annu Rev Biochem 68: 729-777, 1999.

53. Goldshmidt O, Nadav L, Aingorn H, Irit C, Feinstein N, Ilan N, Zamir E, Geiger B, Vlodavsky I and Katz BZ: Human heparanase is localized within lysosomes in a stable form. Exp Cell Res 281: 50-62, 2002.
54. van den Hoven MJ, Rops AL, Vlodavsky I, Levidiotis V, Berden JH and van der Vlag J: Heparanase in glomerular diseases. Kidney Int 72: 543-548, 2007.
55. Gaskin SM, Soares Da Costa TP and Hulett MD: Heparanase: Cloning, function and regulation. Adv Exp Med Biol 1221: 189-229, 2020.
56. Masola V, Bellin G, Gambaro G and Onisto M: Heparanase: A multitasking protein involved in extracellular matrix (ECM) remodeling and intracellular events. Cells 7: 236, 2018.
57. Sanderson RD, Elkin M, Rapraeger AC, Ilan N and Vlodavsky I: Heparanase regulation of cancer, autophagy and inflammation: new mechanisms and targets for therapy. FEBS J 284: 42-55, 2017.
58. David G and Zimmermann P: Heparanase involvement in exosome formation. Adv Exp Med Biol 1221: 285-307, 2020.
59. Simons M and Raposo G: Exosomes-vesicular carriers for intercellular communication. Curr Opin Cell Biol 21: 575-581, 2009.
60. Shteingauz A, Boyango I, Naroditsky I, Hammond E, Gruber M, Doweck I, Ilan N and Vlodavsky I: Heparanase enhances tumor growth and chemoresistance by promoting autophagy. Cancer Res 75: 3946-3957, 2015.
61. Schmidt EP, Overdier KH, Sun X, Lin L, Liu X, Yang Y, Ammons LA, Hiller TD, Suflita MA, Yu Y, *et al*: Urinary glycosaminoglycans predict outcomes in septic shock and acute respiratory distress syndrome. Am J Respir Crit Care Med 194: 439-449, 2016.
62. Masola V, Zaza G, Bellin G, Dall'Olmo L, Granata S, Vischini G, Secchi MF, Lupo A, Gambaro G and Onisto M: Heparanase regulates the M1 polarization of renal macrophages and their crosstalk with renal epithelial tubular cells after ischemia/reperfusion injury. FASEB J 32: 742-756, 2018.
63. Abassi Z, Hamoud S, Hassan A, Khamaysi I, Nativ O, Heyman SN, Muhammad RS, Ilan N, Singh P, Hammond E, *et al*: Involvement of heparanase in the pathogenesis of acute kidney injury: Nephroprotective effect of PG545. Oncotarget 8: 34191-34204, 2017.
64. Masola V, Zaza G, Gambaro G, Onisto M, Bellin G, Vischini G, Khamaysi I, Hassan A, Hamoud S, Nativ O, *et al*: Heparanase: A potential new factor involved in the renal epithelial mesenchymal transition (EMT) induced by ischemia/reperfusion (I/R) Injury. PLoS One 11: e0160074, 2016.
65. Abu-Tayeh Suleiman H, Said S, Ali Saleh H, Gamliel-Lazarovich A, Haddad E, Minkov I, Zohar Y, Ilan N, Vlodavsky I, Abassi Z and Assady S: Heparanase increases podocyte survival and autophagic flux after adriamycin-induced injury. Int J Mol Sci 23: 12691, 2022.
66. Ilan N, Elkin M and Vlodavsky I: Regulation, function and clinical significance of heparanase in cancer metastasis and angiogenesis. Int J Biochem Cell Biol 38: 2018-2039, 2006.
67. Parish CR, Freeman C and Hulett MD: Heparanase: A key enzyme involved in cell invasion. Biochim Biophys Acta 1471: M99-M108, 2001.
68. Secchi MF, Masola V, Zaza G, Lupo A, Gambaro G and Onisto M: Recent data concerning heparanase: Focus on fibrosis, inflammation and cancer. Biomol Concepts 6: 415-421, 2015.
69. Vlodavsky I, Beckhove P, Lerner I, Pisano C, Meirovitz A, Ilan N and Elkin M: Significance of heparanase in cancer and inflammation. Cancer Microenviron 5: 115-132, 2012.
70. Vreys V and David G: Mammalian heparanase: What is the message? J Cell Mol Med 11: 427-452, 2007.
71. Sanderson RD, Bandari SK and Vlodavsky I: Proteases and glycosidases on the surface of exosomes: Newly discovered mechanisms for extracellular remodeling. Matrix Biol 75-76: 160-169, 2019.
72. Xavier RJ and Podolsky DK: Unravelling the pathogenesis of inflammatory bowel disease. Nature 448: 427-434, 2007.
73. Belmiro CL, Souza HS, Elia CC, Castelo-Branco MT, Silva FR, Machado RL and Pavão MS: Biochemical and immunohistochemical analysis of glycosaminoglycans in inflamed and non-inflamed intestinal mucosa of patients with Crohn's disease. Int J Colorectal Dis 20: 295-304, 2005.
74. Abassi Z and Goligorsky MS: Heparanase in acute kidney injury. Adv Exp Med Biol 1221: 685-702, 2020.
75. Axelsson J, Xu D, Kang BN, Nussbacher JK, Handel TM, Ley K, Sriramarao P and Esko JD: Inactivation of heparan sulfate 2-O-sulfotransferase accentuates neutrophil infiltration during acute inflammation in mice. Blood 120: 1742-1751, 2012.
76. Götte M: Syndecans in inflammation. FASEB J 17: 575-591,2003.
77. Carter NM, Ali S and Kirby JA: Endothelial inflammation: The role of differential expression of N-deacetylase/N-sulphotransferase enzymes in alteration of the immunological properties of heparan sulphate. J Cell Sci 116(Pt 17): 3591-3600, 2003.
78. Uchimido R, Schmidt EP and Shapiro NI: The glycocalyx: A novel diagnostic and therapeutic target in sepsis. Crit Care 23: 16, 2019.
79. Becker BF, Jacob M, Leipert S, Salmon AH and Chappell D: Degradation of the endothelial glycocalyx in clinical settings: Searching for the sheddases. Br J Clin Pharmacol 80: 389-402, 2015.
80. Lupu F, Kinasewitz G and Dormer K: The role of endothelial shear stress on haemodynamics, inflammation, coagulation and glycocalyx during sepsis. J Cell Mol Med 24: 12258-12271, 2020.
81. Ponticelli C: Ischaemia-reperfusion injury: A major protagonist in kidney transplantation. Nephrol Dial Transplant 29: 1134-1140, 2014.
82. Bayam E, Kalçık M, Gürbüz AS, Yesin M, Güner A, Gündüz S, Gürsoy MO, Karakoyun S, Cerşit S, Kılıçgedik A, *et al*: The relationship between heparanase levels, thrombus burden and thromboembolism in patients receiving unfractionated heparin treatment for prosthetic valve thrombosis. Thromb Res 171: 103-110, 2018.
83. Masola V, Gambaro G, Tibaldi E, Brunati AM, Gastaldello A, D'Angelo A, Onisto M and Lupo A: Heparanase and syndecan-1 interplay orchestrates fibroblast growth factor-2-induced epithelial-mesenchymal transition in renal tubular cells. J Biol Chem 287: 1478-1488, 2012.
84. Jiang P and Mizushima N: Autophagy and human diseases. Cell Res 24: 69-79, 2014.
85. He C and Klionsky DJ: Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet 43: 67-93, 2009.
86. Singh R and Cuervo AM: Autophagy in the cellular energetic balance. Cell Metab 13: 495-504, 2011.
87. Melk A, Baisantry A and Schmitt R: The yin and yang of autophagy in acute kidney injury. Autophagy 12: 596-597, 2016.
88. Kim WY, Nam SA, Song HC, Ko JS, Park SH, Kim HL, Choi EJ, Kim YS, Kim J and Kim YK: The role of autophagy in unilateral ureteral obstruction rat model. Nephrology (Carlton) 17: 148-159, 2012.
89. Zhang M, Sui W, Xing Y, Cheng J, Cheng C, Xue F, Zhang J, Wang X, Zhang C, Hao P and Zhang Y: Angiotensin IV attenuates diabetic cardiomyopathy via suppressing FoxO1-induced excessive autophagy, apoptosis and fibrosis. Theranostics 11: 8624-8639, 2021.
90. Jin H and Zhou S: The functions of heparanase in human diseases. Mini Rev Med Chem 17: 541-548, 2017.
91. White E: Deconvoluting the context-dependent role for autophagy in cancer. Nat Rev Cancer 12: 401-410, 2012.
92. Saiki S, Sasazawa Y, Imamichi Y, Kawajiri S, Fujimaki T, Tanida I, Kobayashi H, Sato F, Sato S, Ishikawa K, *et al*: Caffeine induces apoptosis by enhancement of autophagy via PI3K/Akt/mTOR/p70S6K inhibition. Autophagy 7: 176-187, 2011.
93. Ferro V, Dredge K, Liu L, Hammond E, Bytheway I, Li C, Johnstone K, Karoli T, Davis K, Copeman E and Gautam A: PI-88 and novel heparan sulfate mimetics inhibit angiogenesis. Semin Thromb Hemost 33: 557-568, 2007.
94. Rabelink TJ, van den Berg BM, Garsen M, Wang G, Elkin M and van der Vlag J: Heparanase: Roles in cell survival, extracellular matrix remodelling and the development of kidney disease. Nat Rev Nephrol 13: 201-212, 2017.
95. Suchorska WM and Lach MS: The role of exosomes in tumor progression and metastasis (Review). Oncol Rep 35: 1237-1244, 2016.
96. Oosthuyzen W, Sime NE, Ivy JR, Turtle EJ, Street JM, Pound J, Bath LE, Webb DJ, Gregory CD, Bailey MA and Dear JW: Quantification of human urinary exosomes by nanoparticle tracking analysis. J Physiol 591: 5833-5842, 2013.
97. Petrik J and Seghatchian J: Big things from small packages: The multifaceted roles of extracellular vesicles in the components quality, therapy and infection. Transfus Apher Sci 55: 4-8, 2016.
98. Conlan RS, Pisano S, Oliveira MI, Ferrari M and Mendes Pinto I: Exosomes as reconfigurable therapeutic systems. Trends Mol Med 23: 636-650, 2017.

99. Essandoh K, Yang L, Wang X, Huang W, Qin D, Hao J, Wang Y, Zingarelli B, Peng T and Fan GC: Blockade of exosome generation with GW4869 dampens the sepsis-induced inflammation and cardiac dysfunction. Biochim Biophys Acta 1852: 2362-2371, 2015.
100. Kanki M, Moriguchi A, Sasaki D, Mitori H, Yamada A, Unami A and Miyamae Y: Identification of urinary miRNA biomarkers for detecting cisplatin-induced proximal tubular injury in rats. Toxicology 324: 158-168, 2014.
101. Viñas JL, Spence M, Porter CJ, Douvris A, Gutsol A, Zimpelmann JA, Campbell PA and Burns KD: micro-RNA-486-5p protects against kidney ischemic injury and modifies the apoptotic transcriptome in proximal tubules. Kidney Int 100: 597-612, 2021.
102. Sun J, Sun X, Chen J, Liao X, He Y, Wang J, Chen R, Hu S and Qiu C: microRNA-27b shuttled by mesenchymal stem cell-derived exosomes prevents sepsis by targeting JMJD3 and downregulating NF-κB signaling pathway. Stem Cell Res Ther 12: 14, 2021.
103. Zhang R, Zhu Y, Li Y, Liu W, Yin L, Yin S, Ji C, Hu Y, Wang Q, Zhou X, *et al*: Human umbilical cord mesenchymal stem cell exosomes alleviate sepsis-associated acute kidney injury via regulating microRNA-146b expression. Biotechnol Lett 42: 669-679, 2020.
104. Juan CX, Mao Y, Cao Q, Chen Y, Zhou LB, Li S, Chen H, Chen JH, Zhou GP and Jin R: Exosome-mediated pyroptosis of miR-93-TXNIP-NLRP3 leads to functional difference between M1 and M2 macrophages in sepsis-induced acute kidney injury. J Cell Mol Med 25: 4786-4799, 2021.
105. Lv LL, Feng Y, Wu M, Wang B, Li ZL, Zhong X, Wu WJ, Chen J, Ni HF, Tang TT, *et al*: Exosomal miRNA-19b-3p of tubular epithelial cells promotes M1 macrophage activation in kidney injury. Cell Death Differ 27: 210-226, 2020.
106. Thompson CA, Purushothaman A, Ramani VC, Vlodavsky I and Sanderson RD: Heparanase regulates secretion, composition, and function of tumor cell-derived exosomes. J Biol Chem 288: 10093-10099, 2013.
107. Roucourt B, Meeussen S, Bao J, Zimmermann P and David G: Heparanase activates the syndecan-syntenin-ALIX exosome pathway. Cell Res 25: 412-428, 2015.
108. Bernfield M and Sanderson RD: Syndecan, a developmentally regulated cell surface proteoglycan that binds extracellular matrix and growth factors. Philos Trans R Soc Lond B Biol Sci 327: 171-186, 1990.
109. Baietti MF, Zhang Z, Mortier E, Melchior A, Degeest G, Geeraerts A, Ivarsson Y, Depoortere F, Coomans C, Vermeiren E, *et al*: Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. Nat Cell Biol 14: 677-685, 2012.
110. Bandari SK, Purushothaman A, Ramani VC, Brinkley GJ, Chandrashekar DS, Varambally S, Mobley JA, Zhang Y, Brown EE, Vlodavsky I and Sanderson RD: Chemotherapy induces secretion of exosomes loaded with heparanase that degrades extracellular matrix and impacts tumor and host cell behavior. Matrix Biol 65: 104-118, 2018.
111. Cummings JJ, Shaw AD, Shi J, Lopez MG, O'Neal JB and Billings FT IV: Intraoperative prediction of cardiac surgery-associated acute kidney injury using urinary biomarkers of cell cycle arrest. J Thorac Cardiovasc Surg 157: 1545-1553.e5, 2019.
112. Parikh CR, Thiessen-Philbrook H, Garg AX, Kadiyala D, Shlipak MG, Koyner JL, Edelstein CL, Devarajan P, Patel UD, Zappitelli M, *et al*: Performance of kidney injury molecule-1 and liver fatty acid-binding protein and combined biomarkers of AKI after cardiac surgery. Clin J Am Soc Nephrol 8: 1079-1088, 2013.
113. Nakamura T, Sugaya T, Node K, Ueda Y and Koide H: Urinary excretion of liver-type fatty acid-binding protein in contrast medium-induced nephropathy. Am J Kidney Dis 47: 439-444, 2006.
114. Mori K, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, Schmidt-Ott KM, Chen X, Li JY, Weiss S, *et al*: Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Invest 115: 610-621, 2005.
115. Chen S, He Y, Hu Z, Lu S, Yin X, Ma X, Lv C and Jin G: Heparanase mediates intestinal inflammation and injury in a mouse model of sepsis. J Histochem Cytochem 65: 241-249, 2017.
116. Kiyan Y, Tkachuk S, Kurselis K, Shushakova N, Stahl K, Dawodu D, Kiyan R, Chichkov B and Haller H: Heparanase-2 protects from LPS-mediated endothelial injury by inhibiting TLR4 signalling. Sci Rep 9: 13591, 2019.
117. McKenzie E, Tyson K, Stamps A, Smith P, Turner P, Barry R, Hircock M, Patel S, Barry E, Stubberfield C, *et al*: Cloning and expression profiling of Hpa2, a novel mammalian heparanase family member. Biochem Biophys Res Commun 276: 1170-1177, 2000.
118. Pinhal MAS, Melo CM and Nader HB: The good and bad sides of heparanase-1 and heparanase-2. Adv Exp Med Biol 1221: 821-845, 2020.
119. Bashkin P, Doctrow S, Klagsbrun M, Svahn CM, Folkman J and Vlodavsky I: Basic fibroblast growth factor binds to subendothelial extracellular matrix and is released by heparitinase and heparin-like molecules. Biochemistry 28: 1737-1743, 1989.