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REVIEW

Small leucine rich proteoglycans in host immunity and renal diseases

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Abstract

The small leucine rich proteoglycans (SLRPs), structurally consisting of protein cores and various glycosaminoglycan side chains, are grouped into five classes based on common structural and functional properties. Besides being an important structural component of extracellular matrix (ECM), SLRPs have been implicated in the complex network of signal transduction and host immune responses. The focus of this review is on SLRPs in host immunity. Because host immunity plays an important part in the pathogenesis of renal diseases, the role of SLRPs in this set of diseases will also be discussed.

Keywords SLRPs · TLR 2/4 · Host immunity · Renal diseases

Abbreviations

SLRP	Small leucine rich proteoglycans
ECM	Extracellular matrix
LRR	Leucine rich repeat
PAMP	Pathogen associated molecular pattern
DAMP	Danger associated molecular pattern
HIF-2 α	Hypoxia-inducible factor 2α
SLE	Systemic lupus erythematosus
RANTES	Regulated upon activation, normal T cell expressed and secreted
MyD88	Myeloid differentiation factor 88
TRIF β	TIR-domain-containing adaptor-inducing interferon β
TLR	Toll-like receptor
TNF α	Tumor necrosis factor α
MIP	Macrophage inflammatory protein
NLRP3	NLR family, pyrin domain containing 3
NOX	NADPH oxidases
ROS	Reactive oxygen species
TGF	Transforming growth factor
miR	Micro-RNA
PDCD	Programmed cell death protein
MCP-1	Monocyte chemoattractant protein-1

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Introduction

The small leucine rich proteoglycans (SLRPs), named after their relatively small size and the leucine rich repeats (LRR) in their structures, consist of two main structural components: protein cores and various glycosaminoglycan (GAG) side chains, which form decorin, biglycan, and lumican etc (Dellett et al. 2012; Schaefer and Iozzo 2008). The SLRP family currently has 17 members that are grouped into five distinct classes based on their conservation and homology at the protein and genomic levels, the number of the LRRs, the spacing of the N-terminal cysteine residues in the protein cores, and their chromosomal organization (Fig. 1) (Dellett et al. 2012; Schaefer and Iozzo 2008). The unique structural characteristics of GAG types provide some of the structural basis for the multitude of the biological functions of SLRPs (Theocharis et al. 2010). So far, biglycan and decorin from class I are among the best studied SLRPs in a variety of biological and pathological processes (Dellett et al. 2012; De Felice et al. 2003; Gubbiotti et al. 2015). Besides being an important component of ECM, SLRPs have been implicated in cell proliferation and migration (Dellett et al. 2012; Schaefer and Iozzo 2008; Kalamajski and Oldberg 2009; Keene et al. 2000; Kresse et al. 1997). Recent studies also demonstrate that SLRP family members are involved in different signaling pathways including TGF-β/Nodal/Smad2

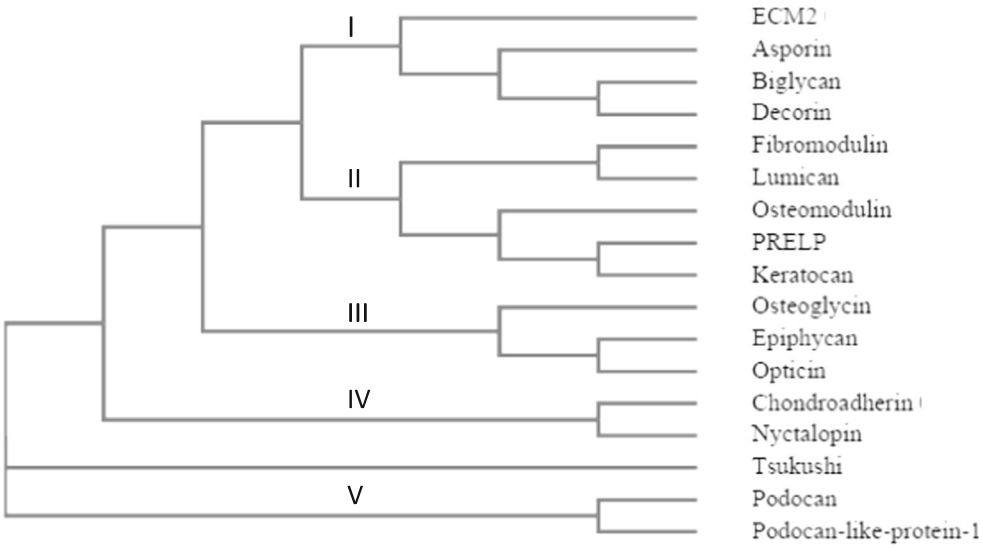

Fig. 1 Phylogenetic tree of the human small leucine-rich repeat proteoglycan (SLRP) family. The phylogenetic tree of the growing human SLRP protein family is generated by multiple sequence alignment using ClustalW2 from the European Bioinformatics Institute. Horizontal distances of the bars are proportional to the predicted evolutionary distance of the available human SLRP sequences

pathway, BMP/Smad1 pathway, EGF pathway, MAPK/FGF pathway, TLR pathway, purinergic pathway and mTOR signaling pathway, indicating an essential role of this family in coordinating other important cellular processes such as fibrosis, autophagy and host immune responses etc (Dellett et al. 2012; Gubbiotti et al. 2015; Babelova et al. 2009; Schaefer et al. 2007; Goldoni et al. 2009; Kou et al. 2010; Tomoeda et al. 2008; Albig et al. 2007; Chen et al. 2011; Nikitovic et al. 2011; Rehn et al. 2006, 2008; Ohta et al. 2011, 2006; Kuriyama et al. 2006; Morris et al. 2007; Iozzo 2015; Schaefer et al. 2017). With more and more studies focused on this family in recent years, the category of the physiological functions and pathological roles of SLPRs are involving rapidly. Current review will specifically focus on the role of SLRPs in host immune responses. Because host immune responses play an important part in the pathogenesis of renal diseases, the role of SLRPs in this set of diseases will also be discussed.

SLRPs and innate immunity

SLRPs and TLR 2/4 signaling pathway

The leucine-rich repeat motifs in the core protein of SLRPs and the structural similarity between SLRPs and the pathogen associated molecular patterns (PAMPs) suggest that SLRPs play a role in host immunity (Shao et al. 2012; Schaefer et al. 2002, 2005; Wu et al. 2007). Indeed, certain SLRPs such as biglycan were described as "analogous to PAMPs" in some studies due to their ability to induce innate immune response by their own without the need of PAMPs (Schaefer et al. 2005; Al Haj Zen et al. 2003).

The best studied signaling pathway in innate immune responses activated by SLRPs is mediated by TLR4/2. As endogenous ligands for TLR 4 and TLR 2, decorin and biglycan stimulate macrophages to produce TNF α, IL-12, and MIP 2 (Schaefer et al. 2005; Moreth et al. 2012). In addition, biglycan itself can activate macrophages and activated macrophages will synthesize and secrete biglycan (Schaefer and Iozzo 2008; Schaefer et al. 2005), indicating a self-amplifying loop involving biglycan exists in the pathway leading to macrophage activation. Biglycan was also reported involved in the activation of NLRP3 inflammasome via the cooperativity of TLR2/TLR4 and P2X receptors leading to the secretion of mature IL-1 β both in a model of non-infectious inflammatory renal injury and in LPS induced sepsis (Babelova et al. 2009), indicating that biglycan may act as a danger associated molecular pattern (DAMP) that is proteolytically released from the ECM upon tissue stress or injury and then turn on host innate and adaptive immune responses (Kalamajski and Oldberg 2009; Schaefer et al. 2005; Nastase et al. 2012; Moreth et al. 2010; Popovic et al. 2011; Schaefer and Iozzo 2012). Recent studies further indicate that through TLR 2/4-NADPH oxidases (NOX) 1/4 -ROS and TLR 4-TRIF/MyD88-NOX 2 axes, biglycan fine-tunes IL-1 β production and maintains immune homeostasis (Schaefer et al. 2017). Interestingly, also through TLR2, biglycan induced the expression of hypoxia-inducible factor 2α (HIF-2α) resulting in increased erythropoietin production in the liver and kidney of a liver-specific, biglycan transgenic mouse model and subsequent enhanced production of erythrocytes (Frey et al. 2017), which potentially is related to inflammation and tumor progression. Signaling pathways through TLR2/4 by biglycan and decorin are summarized in Fig. 2.

Also through TLR4 pathway, another SLRP family member—lumican was found protective against Gram negative bacterial infection, as indicated that $Lum^{-/-}$ peritoneal

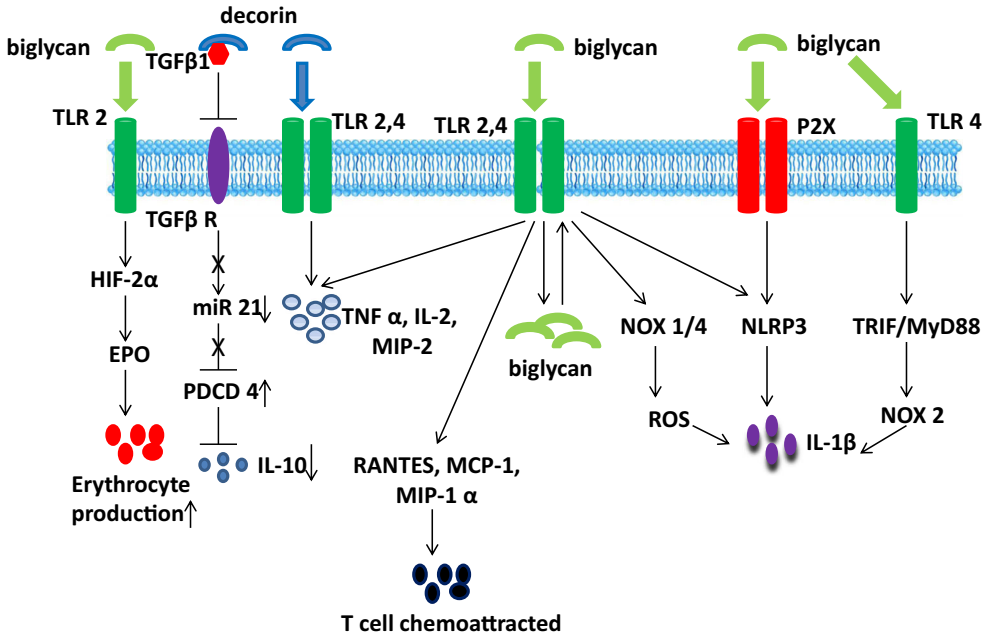

Fig. 2 Decorin and biglycan participate in multiple signaling pathways of innate and adaptive immune responses. As endogenous ligands for TLR 4 and TLR 2, decorin and biglycan stimulate macrophages to produce TNF α, IL-12, and MIP 2. In addition, biglycan itself can activate macrophages and activated macrophages will synthesize and secrete biglycan. Via the cooperativity of TLR2/TLR4 and P2X receptor biglycan is involved in the activation of NLRP3 inflammasome leading to the secretion of mature IL-1 β. IL-1 β production is also fine-tuned by biglycan through TLR 2/4-NOX 1/4 - ROS and TLR 4-TRIF/MyD88-NOX 2 axes. Also through TLR2 biglycan induces HIF-2α expression resulting in increased erythropoietin production and subsequent enhanced production of erythrocytes. Recent studies indicated that TGF-β-miR 21- PDCD 4-IL 10 signaling pathway participated in the post-transcriptional inhibition of IL-10 expression by biglycan. By inducing the secretion of RANTES, MCP-1, and MIP-1 α biglycan chemoattracted T cells to the sites of inflammation through TLR 2/4 signaling. TLR, toll-like receptor; TNF α, tumor necrosis factor α; MIP, macrophage inflammatory protein; NLRP3, NLR family, pyrin domain containing 3; NOX, NADPH oxidases; ROS, reactive oxygen species; TRIF: TIR-domain-containing adaptor-inducing interferon; MyD: myeloid differentiation factor; RANTES: regulated upon activation, normal T cell expressed and secreted; HIF-2 α: hypoxia-inducible factor 2α; TGF, transforming growth factor; miR, micro-RNA; PDCD: programmed cell death protein; MCP-1, monocyte chemoattractant protein-1

macrophages lost the capacity to phagocytoze non-opsonized Gram negative *E. coli* and *P. aeruginosa* in vitro (Shao et al. 2012; Wu et al. 2007). Interestingly, Chakravarti's group showed some different results when they challenged the $Lum^{-/-}$ mice with LPS. They found that the $Lum^{-/-}$ mice were hyporesponsive to LPS-induced septic shock with poor induction of pro-inflammatory cytokines in the serum and a survival benefit was observed in the scenario of LPS challenge (Al Haj Zen et al. 2003). In the same study the authors also reported that challenging $Lum^{-/-}$ mice with live *S. typhimurium* didn't lead to any difference in the production of TNF α in the serum of these animals compared with WT animals (Wu et al. 2007). These findings indicate that activation of innate immune responses *in vivo* is a complicated process and interaction between host and the whole bacterial versus LPS alone may be different. Notably, lumican deficiency didn't affect the response of macrophages to other PAMPs suggesting the role of lumican in TLR-4 signaling pathway is specific (Al Haj Zen et al. 2003). However, not all inflammatory responses will cause tissue damage, and some recent data show that DAMPs that ligate TLR 2/4 drive renal regeneration (Anders and Schaefer 2014).

SLRPs and cytokine/chemokine production

SLRP-induced activation of innate immune responses leads to the production of cytokines and chemokines. In macrophages and dendritic cells soluble biglycan induces the expression of CXCL 13, a major chemoattractant for B cells, especially B1 cells, and an important biomarker for the disease activity of systemic lupus erythematosus (SLE), suggesting a role of biglycan in the pathogenesis of autoimmune diseases involving T cell independent and dependent autoantibody production (Nastase et al. 2012; Moreth et al. 2010). Consistent with this finding, biglycan deficient mice were found hyporesponsive to both LPS and zymosan-induced sepsis due to a mitigated inflammatory response that resulted in less end-organ damage.

Lumican also can induce the secretion of pro-inflammtory cytokines that recruit macrophages and neutrophils to the sites of injury (Albig et al. 2007; Vij et al. 2005; Carlson et al. 2007), and lumican deficiency leads to a marked reduction of neutrophil infiltration that impairs wound healing and resolution of inflammatory diseases (Frey et al. 2013; Hayashi et al. 2010; Lohr et al. 2012). When $Lum^{-/-}$ mice were

challenged with *P. aeruginosa,* these mice failed to clear the bacterium from lungs and other tissues, and showed a dramatic increase in mortality.

As lumican and biglycan, decorin facilitates the transcription and translation of pro- inflammatory and most anti-inflammatory cytokines in the absence and presence of LPS. However, IL-10 is an exception: in the absence of LPS both transcription and translation of IL-10 is increased while in the presence of LPS IL-10 mRNA transcription is upregulated but protein translation is suppressed by decorin (Moreth et al. 2012; Merline et al. 2011), indicating the underlying mechanism of this process is far more complicated than just TLR 2/4 signaling. Indeed, recent studies indicated that TGF-β-miR 21-programmed cell death 4 (PDCD 4)-IL 10 signaling pathway also participated in the post-transcriptional inhibition of IL 10 expression (Fig. 2) (Nastase et al. 2018). In human gingival fibroblasts, decorin was found regulating the production of metalloproteinase (MMP)-1, -2, and -3, tissue inhibitors of metalloproteinase (TIMP) -2, and certain cytokines like TGF-β, IL-1β, IL-4 and TNF-α, suggesting decorin was also a part of tissue remodeling process (Al Haj Zen et al. 2003).

SLRPs as a bridge linking innate and adaptive immunity

Besides their direct involvements in innate immunity, SLRPs also act as a bridge linking innate and adaptive immune responses together. Through TLR 2/4 signaling biglycan regulates T cell activities such as chemoattracting T cells to the sites of inflammation by inducing the secretion of regulated upon activation, normal T cell expressed and secreted (RANTES), MCP-1, and MIP-1 α (Fig. 2). In addition by signaling through both TLRs and their adaptor proteins myeloid differentiation factor 88 (MyD 88) and TRIF β (TIR-domain-containing adaptor-inducing interferon β) biglycan facilitates MHC-I and MHC-II restricted T cell cross-priming (Moreth et al. 2012; Nastase et al. 2012; Moreth et al. 2010; Popovic et al. 2011; Kikuchi et al. 2000; Kitaya and Yasuo 2009; Sjoberg et al. 2009). Over-expression of soluble biglycan has markedly enhanced the systemic and renal outcome of SLE by TLR 2/4 dependent chemoattraction of macrophages and T- and B-lymphocytes (Moreth et al. 2010; Frey et al. 2013).

Implications of SLRPs in renal diseases

Studies have indicated that some SLRPs including decorin, biglycan, and lumican have distinct expression patterns in normal and diseased human kidneys (Schaefer et al. 2000, 2002; Schaefer 2011; Stokes et al. 2001, 2000), suggesting that SLRPs may take part in the pathogenesis of renal diseases. In the normal kidney, decorin and lumican mainly express in peritubular mesenchymal cells in tubulointerstitium with trace amount expression in the mesangial cells in glomerulus, while biglycan mainly expresses in peritubular mesenchymal cells and distal tubules in tubulointerstitium and endothelials in glomerulus with trace amount expression in mesangial cells and epithelial cells in glomerulus (Schaefer et al. 2000). In experimental renal injury, the expression of decorin, biglycan and lumican has been localized to glomerulosclerosis lesions and tubulointerstitial fibrosis (Schaefer et al. 1998; Okuda et al. 1990; Diamond et al. 1997; Silverstein et al. 2003). In end stage glomerulosclerosis, these SLRPs strongly accumulated in Bowman's capsule and in areas of fibrous organization of the urinary space, which became progressively more pronounced with the extent of fibrosis, indicating the involvement of these SLRPs in renal diseases (Babelova et al. 2009; Kitaya and Yasuo 2009; Schaefer et al. 2000; Stokes et al. 2001; Ebefors et al. 2011). Besides, decorin and biglycan deposits in fibrotic lesions were co-localized with collagen type I (Stokes et al. 2001), and they have also been localized in glomerular deposits of amyloid A (Moss et al. 1998). Various kidney diseases that different SLRPs were involved in were summarized in Table 1.

Decorin

In an immunohistochemical study of several matrix proteins, decorin was found to be the best predictor of the severity of interstitial fibrosis and renal failure (Lohr et al. 2012; Merline et al. 2011; Schaefer et al. 2000; Diamond et al. 1997; Vleming et al. 1995; De Heer et al. 2000). Urinary excretion of decorin was significantly increased in patients with membranous nephropathy, minimal change disease and IgA nephropathy, and urine decorin in these patients was negatively correlated to creatinine clearance (Schaefer et al. 2000; Kuroda et al. 2004).

Decorin is found having anti-fibrotic activities. Decorin interacts through its protein core with all three forms of TGF-β with dissociation constants in the nanomolar range and neutralizes TGF-β activities in several organs including kidney by interfering with TGF-β signaling (Schaefer 2011; Stokes et al. 2000; Border et al. 1992; Hildebrand et al. 1994; Yamaguchi et al. 1990). Alternatively, binding of TGF-β to decorin may serve as a reservoir by increasing the availability of this cytokine without the need of de novo synthesis at sites of fibrotic injury (Stokes et al. 2000, 2001). On the other hand, chronic exposure to circulating TGF-β caused an up-regulation of decorin in mouse kidney (Mozes et al. 1999). In addition, decorin inhibits connective tissue growth factor (CTGF) signaling in fibroblast, down-regulates microRNA miR-21, and inhibits apoptosis of renal tubular epithelial cells via the IGF type I receptor/Akt signaling pathway (Anders and Schaefer 2014), which all result in the alleviation of interstitial fibrosis (Anders and Schaefer 2014; Merline et al. 2011; Vial et al. 2011; Glowacki et al. 2013).

Table 1 SLRPs in kidney diseases

SLRPs	Kidney diseases	References
Decorin	DN, OKD, GN, IgAN, CGN, MPGN, PKD	(Iozzo 2015; Vij et al. 2005; Kitaya and Yasuo 2009; Schaefer et al. 1998, 2000; Yamaguchi et al. 1990; Mozes et al. 1999; Vial et al. 2011; Glowacki et al. 2013; Mogyorosi and Ziyadeh 1998; Huijun et al. 2005)
Biglycan	DN, MPGN, OKD, IRI, CRAR, LN, IgAN, IAKI, CGN, PKD	(Iozzo 2015; Schaefer et al. 1998, 2000, 2002; Nastase et al. 2018; Kikuchi et al. 2000; Kitaya and Yasuo 2009; Sjoberg et al. 2009; Schaefer 2011; Stokes et al. 2001; Huijun et al. 2005; Isaka et al. 1996; Iozzo and Schaefer 2015; Zeng-Brouwers et al. 2014; Bedke et al. 2007; Wang et al. 2010)
Podocan	HIVAN, CRAR	(Kiss et al. 2010; Hutter et al. 2013)
Lumican	DN, OKD	(Stokes et al. 2000; Huijun et al. 2005; Christensen et al. 2018)
Fibromodulin	DN	(Huijun et al. 2005)

DN Diabetic Nephropathy, *OKD* Obstructed Kidney Disease, *GN* Glomerulonephritis, *MPGN* Mesangioproliferative GN, *IRI* Ischemia/Reperfusion Injury, *LN* Lupus Nephritis, *CRAR* Chronic Renal Allograft Rejection, *HIVAN* HIV-Associated Nephropathy, *IgAN* IgA Nephropathy, *IAKI* Ischemic Acute Kidney Injury, *CGN* Crescentic GN, *PKD* Polycystic Kidney Disease

In diabetic nephropathy (DN), decorin was upregulated in the mesangial cells, and in response to high glucose stimulation decorin was increased in the mesangial and tubular cells cultured in vitro (Brunskill and Potter 2012; Mogyorosi and Ziyadeh 1998). Decorin deficiency, however, resulted in a much more severe DN with increased mesangial matrix expansion, elevated albuminuria, and increased TGF-β bioactivity in mice with streptozotocin induced diabetes, indicating that decorin is protective against DN (Brunskill and Potter 2012). Interestingly, the importance of decorin in DN was further corroborated by Cosmo and his colleagues' finding that decorin gene 179 allelic variant was associated with a slower progression of renal disease in patients with type 1 diabetes (De Cosmo et al. 2002), indicating genetic mechanisms may also be involved in DN pathogenesis.

In unilateral ureteral obstruction (UUO) model, a well established model of renal inflammation and fibrosis, decorin expression became evident 36 hours after ligation and remained up-regulated throughout the whole experiment (Schaefer et al. 2002). Via specific effects on apoptosis through P27 signaling, TGF-β activity and collagen turnover, decorin had profound effects on the course and final outcome of ureteral kidney obstruction (Schaefer et al. 2002). Not so surprisingly, decorin deficient mice showed marked aggravation of renal fibrosis in ureteral obstruction, further stressing the importance of decorin in fibrotic renal disorders (Lohr et al. 2012; Danielson et al. 1997).

Due to its protective effects against fibrosis, several attempts have been made to explore the potential use of decorin in the treatment of fibrotic renal disorders (Border et al. 1992; Danielson et al. 1997; Costacurta et al. 2002; Huijun et al. 2005; Isaka et al. 1996): administration of exogenous decorin or transfection of decorin cDNA into skeletal muscle has been reported alleviating renal clinical and pathological manifestations including reduced proteinuria, ECM accumulation and glomerular TGF-β levels in experimental animal models (Border et al. 1992; Danielson et al. 1997; Isaka et al. 1996); decorin gene transfection in human mesangial cells downregulates genes playing a role in fibrosis such as TGF-β1, collagen IV and fibronectin in this cell type (Costacurta et al. 2002); and *ex vivo* transfer of decorin gene into rat glomerulus via a mesangial cell vector suppressed extracellular matrix accumulation in experimental glomerulonephritis (Huijun et al. 2005). These findings experimentally validate the use of decorin for gene therapy in treating renal diseases. Indeed, decorin deficiency led to the infiltration of large number of biglycan-expressing macrophages in the kidney (Schaefer et al. 2002) in a non-infectious animal model of renal inflammation.

Biglycan

Sequestered in ECM as a potential inflammatory trigger under normal circumstances, biglycan is released from ECM or de novo synthesized by macrophages and launches a sterile inflammatory response upon tissue damage or stress (Iozzo and Schaefer 2015; Hsieh et al. 2017). Enhanced interstitial and to a lesser degree glomerular expression and deposition of biglycan has been described in certain fibrotic renal diseases such as DN and mesangioproliferative glomerulonephritis (Schaefer et al. 2000; Stokes et al. 2000, 2001; Okuda et al. 1990; Schaefer et al. 2001). Several studies in various experimental models of sterile inflammatory kidney diseases such as ischemia/reperfusion injury and chronic renal allograft

rejection also reveal a striking concurrence of biglycan expression and the extent of renal injury (Merline et al. 2009; Moreth et al. 2014). In a transient transgenic mouse model where full length and fully glycanated biglycan was de novo synthesized by hepatocytes, Schaefer et al. found that renal parenchyma was preferentially targeted by circulating soluble biglycan with profound consequences including the sequential recruitment of neutrophils, macrophages and T cells, and the production of CXCL1,CXCL2 , CCL2 and CCL5 in a TLR 2/4 dependent manner (Hsieh et al. 2017; Zeng-Brouwers et al. 2014). Besides TLR 2/4 signaling pathway, involvement of biglycan in oxidative stress and complement activation also plays an important role in renal injury (Babelova et al. 2009; Moreth et al. 2010).

As decorin, biglycan interacts through its protein core with all three isoforms of TGF-β (Schaefer 2011; Stokes et al. 2000; Border et al. 1992; Hildebrand et al. 1994; Yamaguchi et al. 1990). Besides, TGF-β stimulates the expression of biglycan in all renal cell types studied so far in vitro and in vivo (Schaefer et al. 2001, 2002; Schaefer 2011). However, the role of biglycan in fibrosis is not quite well understood as decorin (Babelova et al. 2009; Schaefer 2011; Bedke et al. 2007; Wang et al. 2010; Kiss et al. 2010).

In UUO model, same as decorin, biglycan expression became evident 36 hours after ligation and remained up-regulated throughout the whole experiment, and biglycan up-regulation was even more pronounced in decorin deficient mice, suggesting compensation exists among different SLRPs (Schaefer et al. 2002). Biglycan up-regulation seems protective in UUO model as indicated by the loss of elastic properties of renal tissue evidenced by cystic dilation of Bowman's capsule and proximal tubules as well as hemorrhaging into renal pelvis in the absence of biglycan (Schaefer 2011; Schaefer et al. 2004). However, increased renal biglycan content, which also occurs in all stages of DN (Nastase et al. 2014), has been thought contributing to renal lipid accumulation and the development of DN (Thompson et al. 2011).

By linking innate and adaptive immune responses together through interacting with TLR2/4, biglycan contributes to the pathogenesis of lupus nephritis (LN), and genetic elimination of biglycan in lupus-prone mice improved systemic and renal outcomes by lowering levels of autoantibodies, reducing enlargement of spleen and lymph nodes, and preventing renal damage and albuminuria. In consistency, biglycan overexpression aggravated renal tissue damage and led to organ failure in these mice (Moreth et al. 2010; Schaefer 2011). In human patients with LN, plasma levels of circulating biglycan were elevated 5 fold compared with controls and higher levels of circulating biglycan were associated with albuminuria, increased plasma levels of CXCL13 and renal inflammation and damage (Moreth et al. 2010). These findings clearly indicate that biglycan participates in and aggravates the progression of LN. As in LN, when rats with Thy-1 nephritis were treated with biglycan delivered by a similar way as decorin was applied (Border et al. 1992), more severe glomerular lesions associated with enhanced infiltration of mononuclear cells, overexpression of glomerular α1 chains of collagen I and IV, and elevated albuminuria were developed (Schaefer 2011). All these findings indicate that the role of biglycan in fibrotic renal diseases is complicated and may vary among different etiologies.

Conclusions and future directions

In this review, we summarized and discussed the current knowledge regarding SLRPs in host immunity and renal diseases. From being recognized as just a molecule maintaining the integrity of ECM to currently being known participating in various signaling pathways, SLRPs are found involved in various cellular and disease processes after two decades of research. Armed with more knowledge about this family, we should be able to explore the potential therapeutic strategies in the treatment of the diseases in which different SLRPs are involved.

For the sake of developing future therapeutics, certain questions still remain to be addressed. For example, under normal conditions, the levels of circulating decorin and biglycan are undetectable while during inflammation or injury, their levels are up-regulated. So the questions are what triggers their up-regulation when injury starts and what dampens them when injury goes away. Could the change of their levels in circulation or in urine or in other body fluids serve as a biomarker for predicting the status of disease activity? Are SLRPs involved in other human disease processes not discussed in this review? Indeed, podocan, a member of the class V SLRP family, was reported up-regulated in the sclerotic glomerular lesion of experimental HIV-associated nephropathy (Ross et al. 2003). Besides, it was also found involved in the pathogenesis of coronary heart diseases (Hutter et al. 2013). Other SLRPs including lumican, fibromodulin, and osteoglycin were found participating in the pathogenesis of heart diseases as well (Christensen et al. 2018). Considering the important role of SLPRs in inflammation which is also essential for tumor initiation and growth, it is not surprising that SLRPs take part in tumorigenesis. Indeed, by regulating MMP activities and/or increasing angiogenesis et al, decorin, biglycan and lumican were reported influencing tumor growth and progression (Schaefer et al. 2017; Pietraszek et al. 2014). Influence of SLRP on exsome trafficking and autophagy is an emerging area of research in recent years (Schaefer et al. 2017; Karamanos 2017). Besides, future studies on the complex interactions among SLRPs and the orchestration of their downstream signaling events are needed. In addition, data regarding the functions of the SLRPs other than decorin and biglycan in different cellular and disease processes are sparse,

and studies on them are warranted since functional compensation or redundancy among different SLRPs do exist, and double or even triple knockout models may need for these studies. Obviously, answers to above questions will fasten the discovery and development of new treatment methods.

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