



Key roles for the small leucine-rich proteoglycans in renal and pulmonary pathophysiology[☆]

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ARTICLE INFO

Article history:

Received 21 December 2013

Accepted 28 January 2014

Available online 5 February 2014

Keywords:

Extracellular matrix

Biglycan

Decorin

Cancer

TGF- β

Toll-like receptor

ABSTRACT

Background: Small leucine-rich proteoglycans (SLRPs) are molecules that have signaling roles in a multitude of biological processes. In this respect, SLRPs play key roles in the evolution of a variety of diseases throughout the human body.

Scope of Review: We will critically review current developments in the roles of SLRPs in several types of disease of the kidney and lungs. Particular emphasis will be given to the roles of decorin and biglycan, the best characterized members of the SLRP gene family.

Major Conclusions: In both renal and pulmonary disorders, SLRPs are essential elements that regulate several pathophysiological processes including fibrosis, inflammation and tumor progression. Decorin has remarkable antifibrotic and antitumorigenic properties and is considered a valuable potential treatment of these diseases. Biglycan can modulate inflammatory processes in lung and renal inflammation and is a potential target in the treatment of inflammatory conditions.

General Significance: SLRPs can serve as either treatment targets or as potential treatment in renal or lung disease. This article is part of a Special Issue entitled Matrix-mediated cell behaviour and properties.

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1. Introduction

Small leucine-rich proteoglycans (SLRPs) represent a unique subgroup in the wider class of proteoglycans that have been shown to have, beside their structural function, complex roles in a wide range of extracellular-mediated signaling platforms [1]. SLRPs owe their name

to the small size of their protein cores and to the presence of tandem leucine-rich repeats (LRRs) in their primary structure flanked by cysteine-rich clusters [2–4]. We have proposed a nomenclature encompassing 18 SLRP genes (Table 1), encompassing five distinct classes based on their N-terminal cysteine-rich clusters, C-terminal ear repeats, homology at the protein and genomic structure and chromosomal organization [1,5,6]. Members of the first three, canonical, SLRP classes, carry both the defining characteristics of a proteoglycan, a protein core structure and one or more glycosaminoglycan (GAG) chains [4,7]. We have included two new SLRP classes containing members that are not “true” proteoglycans, as they are not substituted GAG chains, with the exception of chondroadherin [8]. However, in common with class I–III, class IV and V SLRPs possess functional similarity, extracellular localization and overall high homology [1,3].

Following their post-translational modification, SLRPs are secreted into the extracellular space [5] where they play various biological roles by interacting with a wide number of molecular targets. In the extracellular matrix (ECM), SLRPs can either exist in a matrix-bound, sequestered form, or in a soluble form [9–13]. Unfortunately, most of the data collected so far are centered on only a few representative members of this gene family, especially decorin, biglycan, lumican, and fibromodulin, with research concerning the other SLRPs trailing far behind. However, the emerging evidence indicates that SLRPs are essential structural and signaling molecules of the ECM. In their sequestered form, SLRPs serve as regulators of ECM assembly by binding

Abbreviations: AMPK, 5' adenosine monophosphate-activated protein kinase; ASM, airway smooth muscle; CCL, chemokine (C–C motif) ligand; CDKN1A, cyclin-dependent kinase inhibitor 1; COPD, chronic obstructive pulmonary disease; CREB, cAMP response element binding protein; CS, chondroitin sulfate; CTGF/CCN2, connective tissue growth factor; CXCL, chemokine (C–X–C motif) ligand; DS, dermatan sulfate; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; Erk, extracellular signal-regulated kinase; HIF-1 α , hypoxia inducible factor-1 α ; IGF-IR, insulin-like growth factor receptor; KS, keratan sulfate; LRR, leucine-rich repeats; miR-21, microRNA-21; MMP, matrix metalloproteinase; p21^{WAF1}, cyclin-dependent kinase inhibitor 1; PDCD4, programmed cell death 4; Peg3, paternally expressed gene 3; RTK, receptor tyrosine kinases; SLRP, small leucine-rich proteoglycan; TGF- β , transforming growth factor β ; TGF- β RI, TGF- β receptor; TLR, Toll-like receptor; TNF, tumor necrosis factor; TSP-1, thrombospondin 1; VEGFR, vascular endothelial growth factor receptor

[☆] This article is part of a Special Issue entitled Matrix-mediated cell behaviour and properties.

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Table 1
Members of the SLRP family: classification and main characteristics.

SLRP class	SLRP name	Molecular weight (kDa)	GAG chains
Class I	Asporin	43.2	–
	Biglycan	41.6	CS/DS
	Decorin	39.7	CS/DS
	ECM-2	79.8	–
	ECMX	64.2	–
Class II	Fibromodulin	43.2	KS
	Keratocan	40.5	KS
	Lumican	38.4	KS
	PRELP	43.8	KS
	Osteoadherin	49.5	KS
Class III	Epiphykan	36.6	CS/DS
	Opticin	37.3	–
	Osteoglycin	33.9	KS
Class IV	Chondroadherin	40.5	–
	Nyctalopin	52.0	–
	Tsukushi	37.8	–
Class V	Podocan	69.0	–
	Podocan-like-protein-1	56.5	–

The molecular weight of the unmodified protein core is given for the *Homo sapiens* SLRPs. GAG chains denoted are keratan sulfate (KS), chondroitin sulfate (CS) or dermatan sulfate (DS). A line denotes SLRPs with no or unknown GAG chains.

collagen fibrils, primarily through their LRRs [6,14–20]. Additionally, matrix-bound SLRPs have been shown to be capable of sequestering several molecules, such as growth factors, in the ECM [21–23], thereby inactivating them. As soluble molecules in the ECM, SLRPs play an important role in cell signaling processes, by interacting with several receptors, such as Toll-like receptors (TLR) -2 and -4 [24,25], vascular endothelial growth factor receptor (VEGFR) [26], epidermal growth factor receptor (EGFR) [27], insulin-like growth factor receptor (IGF-IR) [28], integrins [29–33], low density lipoprotein receptor-related proteins [34,35] or hepatocyte growth factor (HGF) receptor (Met) [36,37].

Many of the breakthroughs so far have been the result of studies on mouse models deficient in SLRP genes. Decorin deficiency affects collagen fibril morphology and causes skin fragility [38–40], disrupts angiogenesis [41], alters lung morphology [42] and causes the formation of intestinal tumors [43]. Biglycan-deficient mice suffer as well from collagen fibril abnormalities and further show a propensity to increased bone fragility [23,40,44–47]. In fibromodulin deficient mice additional collagen fibril abnormalities [48] are accompanied by impaired alveolar bone formation [49] and delayed wound closure [50], while lumican deficiency causes skin fragility and reduced corneal transparency [51]. In keratocan deficient mice, corneal transparency remains normal, but the mice suffer subtle alterations in the cornea [52]. Finally, epiphykan deficient mice suffer from abnormal bone development and arthrosis [53].

There have been numerous comprehensive reviews on the biology of SLRPs [4–6,8,9,54–61]. Thus, in this review, we will focus on the SLRP roles in renal and pulmonary pathophysiology. We have chosen to address issues of SLRP involvement in renal and lung diseases as the two organs are closely related, and abnormalities in lung function can result from renal disease [62–65].

2. SLRPs in renal diseases

2.1. Role of SLRPs in renal fibrosis

Chronic renal disease frequently leads to renal fibrosis [66–68]. This process involves excessive accumulation of ECM components, leading to glomerulosclerosis, tubulointerstitial fibrosis, and finally to irreversible loss of renal function and end-stage renal disease. One of the main factors involved in the triggering of fibrosis is the transforming growth factor β (TGF- β) cytokine. TGF- β is normally secreted in the glomerulus by podocytes and mesangial cells [69]. In response to different stimuli such as angiotensin, proteinuria, hypoxia or renal damage, TGF- β is

activated and induces fibrosis through different mechanisms, of which the most documented is Smad2/3 signaling [69], although non-Smad pathways are also important [70]. Since the original discovery that Chinese hamster ovary cells are growth suppressed by soluble decorin and that this is secondary to a decorin-mediated TGF- β block [71], and since the demonstration that decorin can protect against renal fibrosis [72], it has become apparent that decorin has remarkable antifibrotic properties [73–76], with potential utilization of decorin as an antifibrotic treatment [77].

In the normal kidney, decorin is secreted by renal fibroblasts, and exists mainly in the peritubular space, with trace amounts present in the glomerular space [78,79]. In fibrotic renal disease, decorin increases and accumulates in areas of tubulointerstitial fibrosis [80–82]. Such a response might suggest that decorin contributes to the development of renal fibrosis. However, while *Dcn*^{−/−} mice do not show any overt renal phenotype, *Dcn*^{−/−} mice with unilateral ureteral obstruction (UUO), a model of renal inflammation and fibrosis, show an aggravated fibrotic response vis-à-vis wild-type mice [83]. The mechanism for this exacerbated fibrosis includes an early apoptosis loss of tubular epithelial cells before upregulation of TGF- β [83]. Additionally, *Dcn*^{−/−} diabetic mice have a reduced lifespan and develop severe nephropathy, correlated with increased levels of glomerular TGF- β and collagen I [83–85]. Moreover, transfection of exogenous decorin alleviates symptoms of rat anti-Thy1.1 nephritis model, and shows promise as a therapeutic method [86].

While the antifibrotic effect of decorin is uncontested, the underlying mechanism is not totally clear. It is certain that decorin directly interacts with TGF- β [71], a property it shares with biglycan and fibromodulin [87]. Through this interaction, decorin would sequester TGF- β in the extracellular matrix, and protect against its deleterious effects [21]. It has also been shown that decorin can compete with TGF- β for binding to its receptors, TGF- β receptor (TGF- β R)-I and -II [88]. Notably, through interaction with IGF-IR, decorin is able to induce translation of fibrillin-1, which is a regulator of TGF- β availability (Fig. 1) [28,89]. In renal tubular epithelial cells through IGF-IR signaling cascade decorin leads to an inhibition of apoptosis [54]. Thus, the mechanism of action is complex and likely mediated by a differential activity of decorin on multiple RTKs.

Recent studies have revealed that decorin's antifibrotic effects may not be limited to its interaction with TGF- β and its receptors. The cysteine-rich cytokine, connective tissue growth factor (CTGF/CCN2) is a downstream mediator of TGF- β signaling [90] and plays an important role in the evolution of fibrotic disease [91,92]. CTGF is expressed in response to TGF- β in a variety of cell types, including fibroblasts and renal proximal tubule epithelial cells [93], shows mitogenic and chemotactic properties, and induces the synthesis of collagen I, III, integrin β 1 and fibronectin [94].

Remarkably, knockdown of decorin in myoblasts causes increased fibronectin accumulation and sensitivity to CTGF [94]. Concurrently, addition of decorin to CTGF-stimulated myoblasts reduces the levels of collagen III and fibronectin and inhibits actin stress fiber formation. The same inhibitory effect of decorin on CTGF activity can be reproduced in fibroblasts, suggesting that this inhibition could be a general mechanism of CTGF regulation [94]. Indeed, decorin was shown to interact directly with CTGF with high affinity, through LRR12 of its protein core [94]. Moreover, in myoblasts, decorin was shown to be synthesized in response to CTGF. Given the fact that increased CTGF levels are found in renal fibrosis at the sites of tubulointerstitial damage [95], it is likely that decorin/CTGF interaction is key factor, which could provide a mechanistic explanation for the reported antifibrotic properties of this SLRP in renal pathophysiology.

It is puzzling that biglycan, despite its shared ability with decorin to bind TGF- β *in vitro* [87], lacks antifibrotic activity in the kidney [57,74]. Biglycan is synthesized in response to TGF- β in all renal cell types [83,96–98] and is expressed in the interstitium and glomeruli under fibrotic conditions [79,96,97,99]. While in the healthy kidney, biglycan is most likely eliminated in plasma or proteolytically degraded, in

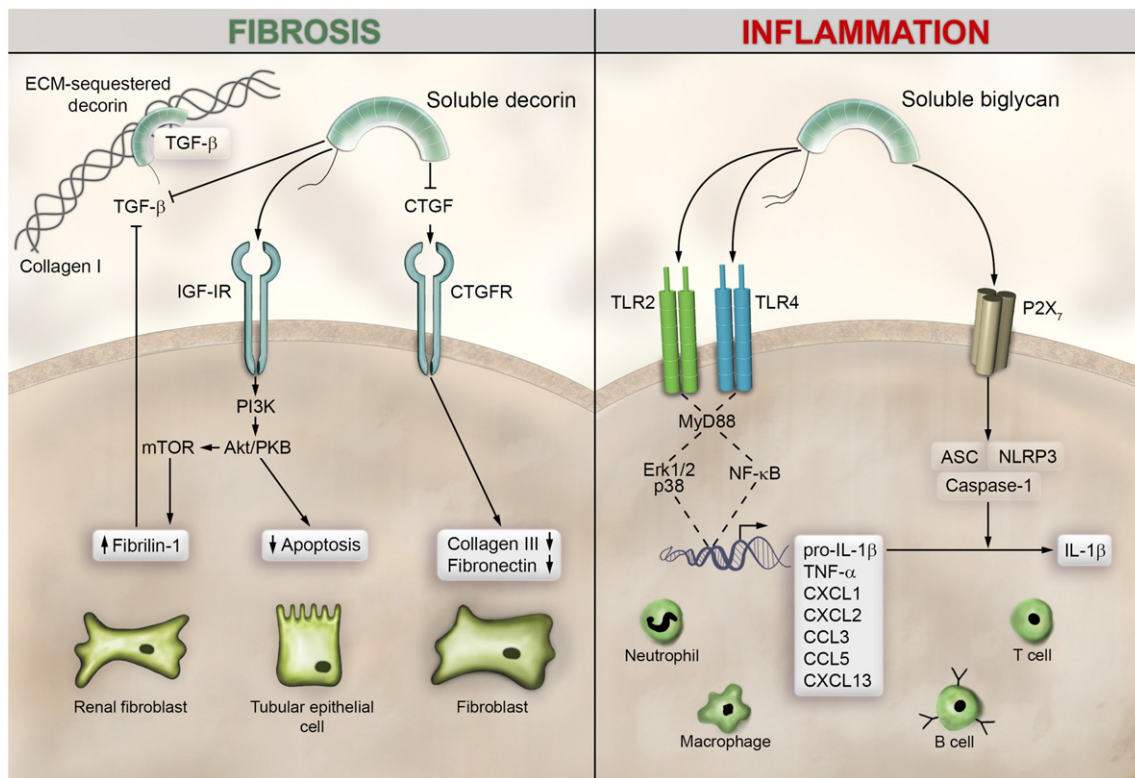


Fig. 1. Decorin and biglycan signaling in fibrosis and inflammation. In renal fibroblasts, through binding to IGF-IR and via the activation of the PI3K and Akt/PKB pathways and mTOR, decorin induces the translation of fibrillin-1, a regulator of TGF-β availability. In tubular epithelial cells decorin reduces apoptosis through interaction with IGF-IR and activation of downstream PI3K/Akt/PKB pathway. Additionally, decorin can bind CTGF (CCN2) and reduce the CTGF-induced levels of collagen III and fibronectin. Soluble biglycan binds to both TLR2 and 4 and via MyD88 activates the Erk, p38 and NF-κB pathways. This leads to the synthesis of pro-IL-1β, TNF-α, and the chemoattractants CXCL1, CXCL2, CCL3 and CCL5. The inflammasome complex NLRP3, ASC and caspase-1 can also be induced by soluble biglycan, leading to activation of caspase-1 which cleaves pro-IL-1β to mature IL-1β. Abbreviations: ASC, apoptosis-associated speck-like protein containing a CARD; CCL, chemokine (C-C motif) ligand; CTGF/CCN2, connective tissue growth factor; CXCL, chemokine (C-X-C motif) ligand; Erk, extracellular-signal-regulated kinase; IGF-IR, insulin-like growth factor type I receptor; IL-1β, interleukin 1β; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; NLRP3, NLR family, pyrin domain-containing 3; PI3K, phosphatidylinositol 3-kinase; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; TNF-α, tumor necrosis factor α.

fibrotic disease it accumulates either due to the increased presence of its collagen-binding partners or due to reduced proteolytic degradation [57]. Interestingly, a role for TLR4, which can be activated by biglycan [24], was found in promoting the evolution of renal fibrosis following UUO [100], in contrast to TLR2, which has no effect on fibrosis [101]. Thus, as biglycan levels are increased in fibrotic tissue, it is possible that the observed effects are a consequence of TLR4 activation by biglycan released or *de novo* synthesized.

Lumican and fibromodulin are both expressed in renal parenchyma, with expression patterns resembling decorin in the case of lumican and biglycan in the case of fibromodulin [57]. Lumican is a component of the endothelial cell surface considered to play a central role in the glomerular barrier [102]. Both lumican and fibromodulin localize to fibrotic regions in diabetic nephropathy [96], though a role for them in the development of renal fibrosis has not yet been reported. However, roles in the development of liver fibrosis for lumican [103], fibromodulin [104] and decorin [105] were recently found. It is therefore likely that lumican and fibromodulin might have similar profibrotic effects in the kidney, and research in this direction would surely provide novel and interesting data.

2.2. SLRPs in renal inflammation and diabetic nephropathy

Several studies have shown that biglycan acts as a proinflammatory danger molecule by signaling through the LRR-containing receptors TLR2 and TLR4 [24,106–108]. For a comprehensive review of the literature on the subject see our recent publication [60]. Below, we will

critically evaluate the main findings regarding the proinflammatory role of biglycan while focusing on its role in kidney inflammatory conditions.

Under conditions of tissue stress or injury biglycan can be released from the extracellular matrix by proteolytic enzymes, such as bone morphogenic protein (BMP)-1, and matrix metalloproteinase (MMP)-2, -3 and -13 [58]. Soluble biglycan then binds to TLR2 and TLR4 and activates the mitogen-activated protein kinase p38, extracellular signal-regulated kinase (Erk), and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) pathways, leading to the secretion of tumor necrosis factor (TNF)-α, in a myeloid differentiation primary response 88 (MyD88) dependent fashion [60]. In turn, this leads to the secretion of a series of chemoattractants for T cells, neutrophils and macrophages, including chemokine (C-X-C motif) ligand 2 (CXCL2), chemokine (C-C motif) ligand 3 (CCL3), CCL2 and CCL5, with the attracted macrophages further synthesizing biglycan, and amplifying the proinflammatory response [60]. Additionally, biglycan can autonomously engage the activation of the NLR family, pyrin domain-containing 3 (NLRP3) inflammasome, and trigger the activation of caspase-1. Caspase-1, in turn, cleaves pro-interleukin-1β (pro-IL-1β) to mature IL-1β (Fig. 1) [106].

In UUO, biglycan is overexpressed in the epithelial cells of distal tubules and collecting ducts, followed by macrophage infiltration [83,101,109]. Biglycan-deficient (*Bgn*^{−/−}) mice show lower levels of activated caspase-1 and mature IL-1β and less renal damage in response to UUO [106]. Biglycan overexpression or accumulation is a feature of several models of kidney disease, such as ischemia/reperfusion injury [110] or chronic renal allograft rejection [111]. In these renal disease

models, a genetic background deficient in either TLR2/4 or MyD88 ameliorates the inflammatory phenotype [110,111]. Notably, administration of rosiglitazone, an agonist of the nuclear receptor peroxisome proliferator-activated receptor (PPAR) gamma, reduces the amount of synthesized biglycan in a rat model of renal transplantation [112]. In addition, administration of rosiglitazone could also block macrophage synthesis of biglycan.

Biglycan is a factor that aggravates experimental lupus nephritis [107], where expression of biglycan positively correlates with expression of CXCL13 and increased albuminuria in Murphy Roths Large (MRL) lupus-prone mice. Moreover, biglycan attracts B- and T-cells to the kidney, by evoking the production of their respective chemoattractants. Consistent with these findings, transient overexpression of circulating soluble biglycan stimulates the expression of CCL2, CCL3 and CCL5 and aggravates the symptoms of murine lupus nephritis. Consequently, biglycan deficiency suppresses disease activity and renal damage [107]. We have recently discovered that transient overexpression of soluble biglycan in mice leads to renal accumulation of biglycan and increased levels of CXCL1, CXCL2, CCL2 and CCL1 [113]. Interestingly, production of CXCL1, CXCL2 and CCL2 occurs through the MyD88 pathway, while production of CCL5 is TIR-domain-containing adapter-inducing interferon β (TRIF)-dependent [113].

Diabetic nephropathy is a complication of diabetes that is the leading cause of end-stage renal failure [114]. Evidence suggests a role for biglycan signaling in the development of diabetic nephropathy. Biglycan upregulation in the kidney occurs in all stages of diabetic nephropathy [96,115]. Diabetic mice exhibit elevation of TGF- β and biglycan levels and high renal lipid retention. The retention of lipids is likely due to the synthesis of abnormal biglycan proteoglycan harboring elongated GAG chains in response to TGF- β [115], as it was previously reported that proteoglycans with large GAG chains have an increased affinity towards low-density lipoprotein (LDL) [116].

Decorin, as biglycan, is overexpressed in the tubulointerstitium in diabetic nephropathy [96]. However, it apparently serves a completely different role, as decorin deficiency enhances murine diabetic nephropathy, with diabetic *Dcn*^{-/-} mice showing increased albuminuria, expanded mesangial matrix, impaired renal function and higher levels of macrophage infiltration compared to wild type animals [84].

Decorin is also a ligand of TLR2 and TLR4, and can stimulate the production of proinflammatory molecules [25]. However, proinflammatory effects of decorin have not been so far reported in the kidney. Quite contrarily, a recent study shows a decrease in decorin levels in glomerulonephritides caused by overexpression of the ovarian-tumor-domain-containing protease OTUB1 [117]. In patients suffering from the most common form of glomerulonephritis, IgA nephropathy, decorin was found to be upregulated in the glomerulus, with a speculated protective role [118]. Human adult renal stem/progenitor cells were shown to promote repair of kidney damage following acute kidney injury, in a process dependent on TLR2, decorin and inhibin-A [119].

The studies summarized above point to a complex regulation of renal fibrosis, with potential compensatory and aggravating mechanisms involving various SLRPs. As we discover new receptors and signaling pathways for SLRPs, we will undoubtedly find this field of research highly rewarding and with potential new targets for disease control or cure.

3. SLRPs in lung disease

3.1. Role of SLRPs in asthma

Asthma is a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing [120]. As SLRPs control both collagen fibrillogenesis and matrix assembly, it is not surprising that these proteoglycans have been implicated in the pathogenesis of asthma as consequences caused by the alteration in

their synthesis, deposition and distribution [121–123]. Earlier studies reported a significantly increased deposition of biglycan and lumican in the subepithelial layer of the airway walls of patients with mild atopic asthma and these changes correlated with increased airway responsiveness [123]. These findings suggest a role for SLRPs in airway wall remodeling and airway mechanics in mild asthma [123]. Indeed, patients with mild asthma present higher biglycan but lower decorin deposition in bronchial mucosa compared to healthy controls [124]. Moreover, decorin and biglycan, together with hyaluronan and versican, are deposited in airways of patients who died of severe asthma, mainly localized in submucosa and around smooth muscle cells [125]. Another study performed in patients dying of severe asthma could show decreased staining of decorin and lumican but not biglycan in the outer area of small airways in asthmatics compared with controls [126]. Later studies described how SLRPs can be excessively deposited in the subepithelial and airway smooth muscle (ASM) layers in patients suffering from both moderate and severe asthma but the staining pattern differs [121]. Endobronchial biopsies show a prominent staining for biglycan and lumican but not decorin in both mild and severe asthmatic patients compared to healthy controls. The ASM layers presented increased biglycan and lumican in moderate asthma compared to the severe condition while in the subepithelial layers biglycan and lumican abundance is similar under both mild and severe conditions of asthma [121]. Few *in vitro* studies are available showing that fibroblasts from the airway of asthmatic patients present more biglycan and decorin compared to cells isolated from normal controls [127,128]. Another study shows that while there is an enhanced biglycan production in centrally derived fibroblasts from asthmatic subjects compared with controls, no difference could be detected in distal airway fibroblasts unless cells were stimulated with TGF- β 1 [129]. Moreover the negative correlation between the alveolar nitric oxide concentration and biglycan production indicates that NO can also reflect the degree of remodeling [129]. In rats, following sensitization to ovalbumin, biglycan and decorin levels are markedly increased in the airway wall, presenting different cellular and subcellular localizations: while biglycan was predominantly detected within the ASM, decorin was detected outside the ASM, in the adventitial layer [130]. The expression changes of the abovementioned SLRPs in asthma as well as their different distribution among the airway layers suggest their potential functional role in asthma [122,130]. Thus, the composition of the extracellular matrix, which has developed during pulmonary remodeling in asthmatic patients, is complex and diverse in terms of SLRP composition, with no single identifiable pattern.

A pathological feature for asthma is “airway remodeling” characterized by structural changes and thickening of the airway wall [130–132] as a result of permanent inflammation and epithelial damage in response to repetitive injury [133]. A key role in airway remodeling is held by the potential of the ASM cells to modulate and interact with the extracellular matrix environment [134–136]. Besides their different features at the expression level decorin has also functional effects on lung mechanics, inflammation, and airway remodeling in allergic asthma [122]. Ovalbumin-challenged *Dcn*^{-/-} mice present more modest lung hyperresponsiveness vis-à-vis wild type. Moreover, these mice do not have significantly increased tissue inflammation and Th2 cytokine message following ovalbumin challenge compared to wild type mice. Furthermore, decorin deficiency determined the absence of collagen deposition and a reduced degree of airway remodeling due to maybe less inflammation [122]. Given that decorin is able to bind TGF- β 1 and to co-localize with this cytokine in bronchial biopsies from asthmatic patients [131], both modest airway hyperresponsiveness and less inflammation found in ovalbumin-sensitized *Dcn*^{-/-} mice might be attributed to higher TGF- β 1 bioavailability [122]. Notably, also biglycan is increased within the airway wall area in ovalbumin-exposed *Dcn*^{-/-} mice [122]. Given that biglycan is predominantly detected within the ASM unlike decorin that is localized to the adventitial layer, the increase of biglycan and the absence of decorin could justify

the limitation of airway remodeling in ovalbumin-challenged *Dcn*^{−/−} mice [122]. Biglycan localization within the ASM layer and surrounding the ASM bundles themselves might contribute to the limitation of the airway narrowing by conferring parallel elastic impedance or radial constraint to ASM shortening [122,137]. Additionally, in the case of decorin, its absence causes a better coupling of the airways and parenchyma and an increased remodeling or thickening of the adventitial layer results in reduced transmission of interdependence forces acting against ASM shortening [122,137]. Furthermore, another study revealed the influence of TGF- β isoforms on OVA-induced decorin deposition in sub-epithelial layer of the airway lumen in mice. Treatment of animals with anti-TGF- β 1 but not with anti-TGF- β 2 inhibits the OVA-induced increase in decorin deposition [138].

An important contributor to asthma airway pathology is the abnormal mechanical strain, which can be sensed by the structural cells of the airway like epithelial cells, fibroblasts and ASM cells [139–141]. A recent study investigated how alterations of biglycan, decorin and collagen and mechanical strain conditions effect the proliferation of the ASM cells isolated from Brown Norway rats challenged with ovalbumin [141]. Both isolated from ovalbumin-sensitized rats or controls, ASM cells seeded on a decorin matrix proliferate slower compared to when they are grown on plastic; the effect was weaker in the case of ovalbumin treated rats. Biglycan has the same effect but only in control cells [141].

3.2. SLRPs in pulmonary infection and sepsis

Pulmonary damage, classified as either acute lung injury or acute respiratory distress syndrome is a common complication and one of the major causes of death following sepsis [142]. The proinflammatory role of biglycan in the progression of sepsis was revealed in one of our earlier studies [24]. Biglycan deficiency improves mouse survival in both LPS- and zymosan-induced sepsis, and reduces the amount of TNF- α in plasma. In wild-type mice, biglycan levels in infiltrating cells of lung parenchyma are increased under septic conditions, as a consequence of biglycan production by macrophages. *In vitro*, exogenous soluble biglycan stimulates macrophages to produce TNF- α and CXCL2, a chemoattractant for macrophages. Consequently, *Bgn*^{−/−} mice have less prevalent immune cell infiltrates in septic lungs [24]. Additionally, biglycan deficiency also lowers levels of mature IL-1 β and active caspase-1 in septic lungs, resulting in less organ damage [106].

Interestingly, decorin is also upregulated in septic lungs and decorin deficiency also ameliorates the outcome of sepsis [25]. Levels of the anti-inflammatory cytokine IL-10 are increased, while levels of TNF- α and IL-12 are reduced in septic lungs of *Dcn*^{−/−} mice. Injection of exogenous decorin in *Dcn*^{−/−} mice subjected to sepsis results in lower levels of IL-10 and increased levels of TNF- α and IL-12 in the lung. This proinflammatory effect of decorin is mediated through interaction with TLR2/4 and production of programmed cell death 4 (PDCD4) [25].

Lumican was recently found to have a critical role in the clearance of bacterial infection [143,144]. *Lum*^{−/−} mice show increased severity of *Pseudomonas aeruginosa* lung infection, manifested by reduced survival and increased pulmonary damage [143]. Lumican is capable of promoting phagocytosis by associating with the bacterial surface as well as with the adapter protein cluster of differentiation 14 (CD14). In the latter interaction, a critical role is played by Tyr20 of lumican, as mutation of this residue to alanine causes a severely reduced effect of lumican on phagocytosis [143].

3.3. Role of SLRPs in pulmonary fibrosis and chronic obstructive pulmonary disease

Idiopathic pulmonary fibrosis, the most common fibrotic lung disease, has a 5-year survival rate of only 20%, and has no effective therapy [145]. A widely used experimental animal of pulmonary fibrosis is based on the use of the cytotoxic drug bleomycin [146]. Intratracheal

administration of bleomycin causes a rapid and robust inflammatory response and increased epithelial apoptosis, followed by resolution of inflammation and ECM deposition, forming areas of fibrosis [146].

In rats with bleomycin-induced pulmonary fibrosis there is a dynamic modulation of various SLRPs, with increased levels of biglycan and fibromodulin [147] and reduced levels of decorin [148]. Decorin's antifibrotic effects are also operational in lung fibrosis, where this SLRP might serve as a powerful treatment for this condition. Indeed, bleomycin-induced lung fibrosis in hamsters can be ameliorated by instillation of decorin, with reduction in both the size of the fibrotic lesions and the number of infiltrating neutrophils [149]. Transient expression of decorin using an intranasal-administered adenoviral vector also reduced the profibrotic effects of bleomycin, without influencing the initial inflammatory response, an effect which was speculated to occur through the inactivation of TGF- β [150]. In a subsequent study, intratracheal administration of an adenoviral vector expressing decorin decreased subpleural fibroproliferation in bleomycin-induced lung fibrosis, while intravenous administration of the same vector had no effect [151]. *In vitro*, transfection of decorin, but not biglycan could block the activity of TGF- β in lung fibroblasts [74]. A similar effect also occurs *in vivo*, where transient overexpression of TGF- β by intranasal injection of an adenoviral vector causes interstitial fibrosis, a process that is significantly attenuated by the concomitant transient expression of decorin, but not biglycan [74]. Thus, decorin delivered as either recombinant proteoglycan or endogenously produced via adenoviral transduction, possesses antifibrotic effects. Whether all the effects can be attributed to its TGF- β -blocking ability needs to be further investigated.

Chronic obstructive pulmonary disease (COPD) is an inflammatory airway disease, characterized by progressive and irreversible decline in lung function caused by airflow obstruction, destruction of parenchyma and emphysema [152]. The primary cause of COPD is exposure to air pollutants, primarily cigarette smoke [152]. Airway remodeling is one of the characteristics of COPD; interestingly, in COPD lungs the ECM is degraded in alveoli but increased in bronchi and bronchioles [153]. Early studies pointed out a reduction in the expression of biglycan and decorin in the peribronchiolar area in patients suffering from severe emphysema, associated with increased levels of TGF- β [154]. Additionally, fibroblasts from isolated from patients with severe emphysema showed reduced decorin production in the supernatant in response to TGF- β [155]. However, single nucleotide polymorphisms in the *Dcn* gene were not found to be a risk factor in the development of COPD [156]. As these results differ from those obtained with patients suffering from milder forms of COPD, where biglycan and decorin levels are not different from controls [136], it is apparent that severe modifications in the ECM occur only in the later stages of COPD.

COPD is characterized by an influx of immune cells in the lung. Interestingly, peripheral blood mononuclear cells isolated from COPD produce higher amounts of anti-decorin IgG in response to stimulation with decorin [157]. Administration of corticosteroids along with bronchodilators such as β 2 agonists is the current treatment method of choice for COPD [158]. Effects of such treatments on SLRP expression show promising results. In an *in vitro* study, fluticasone could induce decorin production by airway fibroblasts from patients with severe COPD, and reverse the negative effects of TGF- β on ECM production in these cells [159]. Additionally, biglycan production is inhibited by fluticasone in both airway and parenchymal fibroblasts. In patients suffering from moderate COPD, administration of corticosteroids increased the density of decorin staining in bronchial tissue [160]. However, treatment with the vasodilator prostacyclin has no effect on biglycan or decorin expression in fibroblasts from COPD patients [161].

3.4. Role of SLRPs in lung cancer

An emerging body of evidence supports the idea that several SLRPs might play a significant role in tumor progression, by affecting both

the composition of the tumor stroma as well as the growth of cancer cells [4,9,59,162,163]. Decorin is the most investigated so far among the SLRPs and represents a potential therapeutic molecule to combat many forms of cancer, particularly due to its ability to interact with many receptor tyrosine kinase (RTKs) and downregulate their activity [163]. Decorin has a potent antitumorigenic effect and is able to repress and attenuate tumor cell proliferation, survival, migration and angiogenesis [59,164]. It is well known that decorin is able to interact with RTKs including EGFR, Met, ErB2/4 or vascular endothelial growth factor receptor (VEGFR2) thereby attenuating the respective signaling pathways (Fig. 2) [1,59]. The first RTK revealed to bind decorin in tumor cells was EGFR [27]. Following decorin binding the receptor dimerizes and is further endocytosed via caveolar-mediated pathway, which leads to translocation into caveosomes and eventually to lysosomal degradation [165] (Fig. 2). In parallel, following decorin binding and EGFR phosphorylation, ERK1/2 are activated, leading to the transcription of the *CDKN1A* gene corresponding to cyclin-dependent kinase inhibitor 1, p21^{WAF1}, thus ultimately leading to growth suppression [163,166] (Fig. 2). Another effect downstream of decorin-mediated EGFR phosphorylation is the activation of caspase-3, which in turn cleaves the intracellular domain of EGFR [167].

Decorin interferes with the Met signaling pathway causing down-regulation and shedding of Met, attenuation of the signaling effects and inhibition of tumor growth [36,37,162]. When Wnt or RTK pathways (EGFR or Met) are activated, Myc is phosphorylated at serine 62

(S62), triggering translocation of Myc to the nucleus where the synthesis of activating enhancer-binding protein (AP4) is induced [162]. AP4 is a transcriptional repressor of *CDKN1A* gene [168] (Fig. 2). At the same time, β -catenin is translocated to the nucleus where it is recruited to and activates lymphoid enhancer-binding factor/T-cell-specific factor (TCF/LEF)-related gene transcription [35,169]. The synthesis of tumor-associated genes such as *c-MYC* and *MYCN* is then induced [162] (Fig. 2). When decorin binds to Met, the above-mentioned pathways are inhibited. Myc is phosphorylated at threonine 58 (T58), known to destabilize Myc and to target it for proteasomal degradation [37] (Fig. 2). The consequent effects are suppression of cell motility, migration and tumor growth, both *in vitro* and *in vivo* [37]. Thus, at least for decorin/Met interaction a partial mechanism has been elucidated. We predict that other SLRPs would also interact with other members of this large RTK family and that these interactions would be important in the pathophysiology of pulmonary and renal diseases.

Decorin is known to play an important role in tumor angiogenesis but its influence in this process remains to be investigated taking into consideration data advocating for both proangiogenic and antiangiogenic roles [162]. However, the studies revealing the proangiogenic role of decorin are described mostly in non-tumorigenic cells [59,170]. Decorin was proved as an angiostatic agent in tumor cells via down-regulation of vascular endothelial growth factor (VEGF) [171]. Recently, Neill et al. observed by PCR array in HeLa cells under normoxia conditions that decorin inhibits the transcription of pro-angiogenic genes

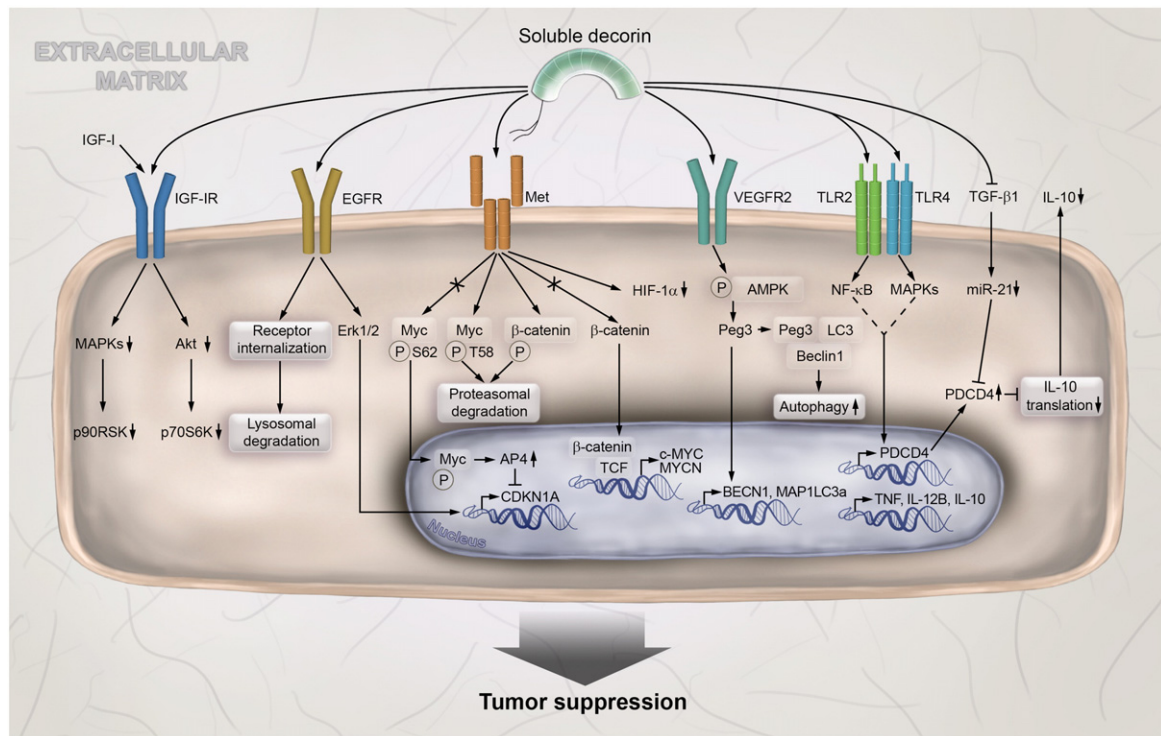


Fig. 2. Decorin's interference with signaling in cancer. In cancer cells, decorin binds to IGF-IR and to its ligand IGF-I at different binding sites and decreases both IGF-I-induced MAPK and Akt pathways activation leading to less level of p90RSK and p70S6K, respectively. Through binding to EGFR, decorin leads to receptor internalization and its lysosomal degradation. Following binding, EGFR gets phosphorylated and Erk1/2 are activated, leading to the transcription of the *CDKN1A* gene corresponding to cyclin-dependent kinase inhibitor 1, p21^{WAF1}. When the HGF receptor Met is activated following Serine62 phosphorylation, Myc is translocated to the nucleus which induced the synthesis of AP4, a repressor for the *CDKN1A* gene. At the same time β -catenin is also translocated to the nucleus where it is recruited to and activates TCF/LEF-related gene transcription and induces the synthesis of tumor-associated genes such as *c-MYC* and *MYCN*. When decorin binds to Met following the phosphorylation of Myc (at Threonine58) and β -catenin, both are triggered to proteasomal degradation. Through Met, decorin inhibits proangiogenic factors such as HIF-1 α . Alternatively, decorin interacts with VEGFR2 thereby leading to rapid phosphorylation of AMPK and increased levels of Peg3 as well as Peg3-dependent expression of autophagy-related genes *BECN1* and *MAP1LC3a*. This mechanism is upstream of autophagy induction under decorin stimulation. Decorin binds TLR2 and TLR4, activates MAPKs and NF- κ B and induces the transcription of the *TNF*, *IL-12B*, *IL-10* and *PDCD4* genes. Decorin-induced PDCD4 leads to translational repression of IL-10. By inhibiting TGF- β signaling, decorin decreases the abundance of oncogenic microRNA-21 (miR-21) and prevents the miR-21-dependent translational repression of PDCD4 and thus reduces the levels of IL-10 protein. Abbreviations: AMPK, 5' adenosine monophosphate-activated protein kinase; AP4, activating enhancer-binding protein; BECN1, Beclin1; CDKN1A, cyclin-dependent kinase inhibitor 1; EGFR, epidermal growth factor receptor; Erk, extracellular-signal-regulated kinase; HGF, hepatocyte growth factor; HIF-1 α , hypoxia inducible factor-1 α ; IGF-I, insulin growth factor type I; IGF-IR, insulin-like growth factor type I receptor; IL, interleukin; MAP1LC3a, microtubule-associated protein 1 light chain 3 alpha; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PDCD4, programmed cell death 4; Peg3, paternally expressed gene 3; TCF/LEF, lymphoid enhancer-binding factor/T-cell-specific factor; TNF- α , tumor necrosis factor; TGF- β , transforming growth factor- β ; VEGFR2, vascular endothelial growth factor receptor.

including *MET*, hypoxia inducible factor-1 α , *HIF-1 α* , and *VEGFA* while upregulating the transcription of anti-angiogenic genes such as metalloproteinase inhibitor 3, *TIMP3* and thrombospondin 1, *THBS1* [172]. Further, the same study reveals that in MDA-MD-231 breast carcinoma cells expressing constitutively active HIF-1 α , decorin reduces the levels of HIF-1 α and *VEGFA* via the Met receptor [172]. In parallel, exogenous decorin triggers the overexpression of angiostatic thrombospondin 1 (TSP-1) and *TIMP3* while inhibiting the expression and activity of pro-angiogenic MMP-9 and MMP-2 [172]. Notably, decorin evokes the rapid release of TSP-1 from quiescent MDA-MB-231 breast carcinoma cells [173]. TSP-1 release is dependent on EGFR signaling, but independent of Met signaling. The mechanism involves the degradation of Ras homolog gene family member A (RhoA) and subsequent inactivation of Rho-associated coiled-coil containing protein kinase 1 (ROCK1) [173].

Recent studies have shown that soluble decorin induces autophagy in human umbilical vein endothelial cells (HUVEC) and in mouse microvascular dermal endothelial cells (MDEC) [26]. At the same time decorin induces the expression of paternally expressed gene 3 (Peg3), which is known as a tumor suppressor, as well as the Peg3-dependent expression of autophagy-related genes *BECN1* and *MAP1LC3a*. In addition, decorin evokes intracytoplasmic colocalization of Peg3, Beclin 1 and LC3 within newly formed autophagosomes [26]. It was shown that the mechanism was downstream of decorin binding to VEGFR2 (Fig. 2) [174]. As a consequence decorin inhibits capillary morphogenesis and endothelial cell migration [26]. Thus, decorin, and perhaps other members of the SLRP family, modulate angiogenesis by evoking a biological process such as autophagy, which could lead to angiostasis.

In bladder cancer cells, decorin binds to IGF-IR and to its ligand IGF-I at different binding sites and differently to EGFR and Met, decorin negatively regulates IGF-I-dependent IGF-IR phosphorylation without affecting receptor protein levels [175]. Downstream of IGF-IR activation the recruitment of insulin receptor substrate 1 (IRS-1) to the receptor is required in order to activate the phosphatidylinositol 3-kinase (PI3K) and Akt pathways, promoting cell proliferation and transformation in normal cells [175]. It has been shown that IGF-I acts as a “scatter factor” in urothelial cancer cells which enhances cell motility and invasion but not cell proliferation [176]. Decorin enhances IGF-I-dependent IRS-1 downregulation upon chronic IGF-I stimulation of tumor cells. It could also inhibit the IGF-I ability to promote migration, lateral motility and invasiveness in cancer cells. Mechanistically, decorin is able to attenuate IGF-I-induced Akt and Erk1/2 pathways and inhibit the downstream targets p70S6K and p90RSK, respectively [175].

Another mechanism was recently proposed regarding the capability of decorin to link inflammation and cancer growth [25]. As previously mentioned in Section 3.2, decorin is able to bind TLR2/4 activating Erk and p38 and inducing the transcription of the *TNF*, interleukin 12B, *IL-12B*, interleukin 10, *IL-10* and *PDCD4* genes (Fig. 2). Decorin- or LPS-induced *PDCD4* leads to translational repression of *IL-10*, an anti-inflammatory cytokine (Fig. 2). LPS induces active TGF- β 1 production that, by signaling through its receptor, promotes the processing of pri-miR-21 to pre-miR-21 and increases the abundance of mature miR-21, a posttranscriptional inhibitor of *PDCD4*. By inhibiting TGF- β signaling, decorin decreases the abundance of oncogenic microRNA-21 (miR-21) and prevents the miR-21-dependent translational repression of *PDCD4* and thus reduces the levels of *IL-10* protein [25] (Fig. 2). In the presence of LPS, decorin stimulates the expression of *PDCD4* through TLR2 and inhibits the LPS-induced activity of TGF- β 1. Tumor xenografts overexpressing decorin present an induced proinflammatory immune response through inhibition of TGF- β 1, down-regulation of miR-21, and increased *PDCD4* abundance [25]. Notably, these findings were independently confirmed by a recent study demonstrating that decorin can be cleaved by MMP-8 and lead to a reduction in tumor growth and lung metastasis formation by MDA-MB-231 (4175) breast cancer cells by inhibiting TGF- β signaling and reducing miR-21 levels [177].

The anti-tumoral effects of decorin in lung cancer were already emphasized in earlier studies showing that in patients with T1 pulmonary adenocarcinoma, TGF- β 1 is primarily associated with central fibrosis [178]. Additionally, when central fibrosis was composed of proliferative connective tissue with weak staining for decorin, cancer cells showed intense staining for TGF- β 1 while when central fibrosis was composed of old fibrotic tissue with dense staining for decorin, cancer cells showed weak staining for TGF- β 1 suggesting the role of decorin as a TGF- β 1 negative regulator in pulmonary adenocarcinoma [178]. Decorin is underexpressed by at least 50% of human lung adenocarcinomas and squamous cell carcinomas [179]. The role for decorin in suppressing pulmonary metastasis from osteosarcoma has also been proposed [180]. Specifically, murine osteosarcoma cells stably expressing decorin are less metastatic than wild-type cells; moreover, *de novo* decorin expression significantly improved the survival of the mice [180]. This study brings into light the potential role of decorin as a novel biological tool for the treatment of pulmonary metastasis [180].

Recently, biglycan has also been found to be abnormally expressed in a number of human tumors such as endometrial [181], pancreatic [182], gastric [183], colorectal [184], adenomatoid odontogenic tumor [185] and ovarian [186] cancer. However, the mechanisms through which biglycan is involved in tumor progression are far from being clear. Interestingly, TGF- β induces biglycan expression in HFL, HFFF2 fibroblasts and the pancreatic cancer cell line PANC-1 [187]. Biglycan, in turn, is able to inhibit growth of TGF- β responsive pancreatic cancer cells by inducing G1-arrest [187]. The biglycan-mediated inhibition of cell growth is accompanied by an increase of p27 and reduction of cyclin A and proliferating cell nuclear antigen, PCNA. Furthermore, endogenous Ras and Erk activation is partly reduced by biglycan *in vitro* [187]. Additionally, an *in vitro* study using oncogene transformation has shown a down-regulation of biglycan expression in both murine and human HER-2/neu oncogene-transformed cells when compared with HER-2/neu(–) cells [188]. Biglycan expression correlates well with reduced growth, wound closure, and migration properties. Biglycan expression was found to be dependent on the protein kinase C (PKC) and cAMP response element binding protein (CREB) [188].

Moreover, biglycan acts as a proangiogenic factor in murine tumor endothelial cells influencing their migration and morphology. Biglycan-induced migration and tube formation are blocked by anti-TLR2 and anti-TLR4 antibodies in biglycan deficient tumor endothelial cells [189]. Additionally, biglycan immunoreactivity is stronger in tumor vessels of patients with colon, lung or liver cancers vis-a-vis healthy patients [189]. Given its role in the development and progression of human cancers and its different expression pattern in different tumors, biglycan could be further evaluated as a biomarker for predicting clinical outcome.

Lumican has also been broadly investigated in cancer with results pointing to an antagonistic role of cancer growth and angiogenesis [162]. However, there are studies that either attribute to lumican a pro-oncogenic agent (in colorectal, pancreatic and lung cancer) as well as that of an anti-oncogenic agent (in osteosarcoma or melanoma) [59,162]. Mechanistically, similarly to decorin, lumican is a soluble tumor suppressor agent that induces p21^{WAF1} and growth inhibition [190]. In mouse embryonic fibroblasts, lumican-mediated p21^{WAF1} induction depends on the p53 pathway and leads to suppression of cyclins A, D1 and E [162,191]. At the same time lumican inhibits cell proliferation and is pro-apoptotic through Fas receptor (CD95)-Fas ligand in cornea [191]. Lumican protein core binds the α 2 I domain of the α 2 β 1 integrin receptor in melanoma cells, thereby inhibiting cell migration [32]. Notably, *Lum*^{–/–} mice harboring pancreatic adenocarcinomas develop higher volume size tumors and exhibit elevated vascular densities compared to wild-type mice [192]. However, lumican inhibits tumor growth and lung metastasis but not angiogenesis in a 4T1 breast cancer model [192].

A recent study described the importance of lumican in patients with lung cancer. Specifically, lumican is >2-fold upregulated in lung cancer

patients compared to healthy subjects using proteomic analysis of serum from lung cancer patients and healthy volunteers [193]. Analysis of the expression of lumican in two types of non-small cell lung cancer revealed different expression patterns. In lung adenocarcinoma, higher levels of lumican could be found in stromal, rather than cancer cells [194]. Contrary to this pattern, in lung squamous cell carcinoma, expression of lumican is higher in cancer cells [194]. Notably, mice intravenously injected with lumican-expressing B16F1 melanoma cells exhibit a decreased number and size of pulmonary metastases and an increase in tumor cell apoptosis when compared to Mock-B16F1 cells-injected mice [195]. In contrast, however, the levels of VEGF and the number of blood vessels within the lung metastases were decreased following lumican overexpression [195]. Thus, the roles of SLRPs in lung cancer are quite complex and require additional experimental research to decipher the specific signaling pathways that could affect the behavior of both primary tumor cells and their microenvironment.

4. Conclusion and future perspectives

A large volume of studies now exist on the roles of SLRPs in the pathogenesis and even treatment of pulmonary and renal diseases. It is, however, likely that our knowledge so far is only a small glimpse into the multitude of functions that these molecules have. Most of the available data are restricted to biglycan and decorin, with more interacting partners and signaling pathways discovered every year. Perhaps the most remarkable conclusion of these studies is that decorin has the potential to be a powerful antifibrotic and antitumoral agent, and we anticipate that its value will be appreciated in clinical trials.

However, it is regrettable that research on the other SLRPs is lacking. While there are a number of studies dealing with lumican and fibromodulin, there are several other SLRPs that have been investigated only in few published studies despite their widespread distribution and regulated developmental expression. Recent studies on lumican, for example, have shown that it also has antitumoral roles, and further research in this direction is worth considering. We believe that given the current knowledge of SLRP biology, future discoveries are on the horizon and could lead to fundamental changes in our understanding of SLRP function and their involvement in various human pathologies.

Acknowledgments

Original research on SLRP biology in the authors' laboratories was supported by the German Research Council (SFB 815, project A5, SFB 1039, project B2, Excellence Cluster ECCPS to L.S., and GRK1172 to M.V.N. and L.S.), LOEWE program Ub-Net (L.S.) and by National Institutes of Health grants RO1 CA39481, RO1 CA47282 and RO1 CA164462 (R.V.I.). We apologize to those researchers whose work could not be cited due to space limitation.

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