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Proteoglycan neofunctions: Regulation of inflammation and autophagy in cancer biology

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Abstract

Inflammation and autophagy have emerged as prominent issues in the context of proteoglycan signaling. In particular, two small, leucine-rich proteoglycans, biglycan and decorin, play pivotal roles in the regulation of these vital cellular pathways and, as such, are intrinsically involved in cancer initiation and progression. In this minireview we will address novel functions of biglycan and decorin in inflammation and autophagy, and analyze new emerging signaling events triggered by these proteoglycans, which directly or indirectly modulate these processes. We will critically discuss the dual role of proteoglycan-driven inflammation and autophagy in tumor biology, and delineate the potential mechanisms through which soluble ECM constituents affect the microenvironment associated with inflammatory and neoplastic diseases.

Graphical Abstract

We critically asses the role of two small, leucine-rich proteoglycans, biglycan and decorin, in inflammation and autophagy. The signaling axes of these two proteoglycans are operative during various stages of cancer initiation and progression. Moreover, we discuss the dual role of proteoglycan-driven inflammation and autophagy in tumor biology, and offer unique roles for these molecules as potential therapeutic agents.

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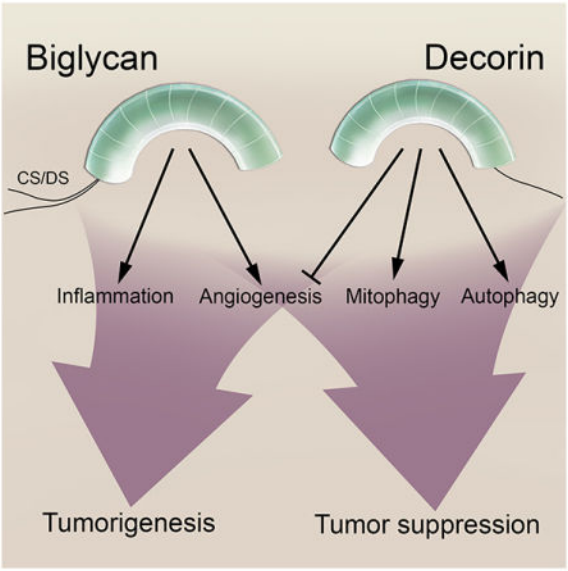
Author contributions

L.S., C.T., M.A.G. and R.V.I. conceived the ideas, wrote the manuscript and created the figures.



Keywords

Small leucine-rich proteoglycans; decorin; biglycan; receptor tyrosine kinase; Toll-like receptors; LC3

Introduction

For decades, the two closely related small, leucine-rich proteoglycans (SLRPs), biglycan and decorin, have been considered as rather structural elements of the extracellular matrix (ECM). For example, biglycan has long been regarded as an important factor for bone mineralization and decorin originally gained recognition for its role in the regulation of collagen fibrillogenesis [1]. However, this paradigm shifted when biglycan and decorin were identified as functional signaling molecules, particularly in the context of inflammation and autophagy regulation. As these processes play a crucial role both in the initiation and progression of tumorigenesis, and as these proteoglycans distinguish themselves further as dynamic players in cell signaling, it has become apparent that biglycan and decorin, and their downstream signaling effectors, might represent druggable therapeutic targets for the treatment of malignant disease. The role of syndecan and heparanase, two key players in cancer progression, is also covered in this thematic minireview series [2,3].

In this review, we provide an inclusive and critical assessment of the roles of biglycan and decorin in autophagy as well as in inflammatory signaling pathways, with a strong emphasis on their functions in the setting of cancer. We will further evaluate the intricate connection between these endogenous matrix constituents and both normal and pathological cellular activity to provide insight into future options for the treatment of cancer and other diseases where inflammation is predominant.

Matrix regulation of endothelial cell autophagy and tumor cell mitophagy

Neovascularization is a long-standing hallmark in the context of cancer progression as the growth of new blood vessels allows the tumor proper to acquire necessary nutrients to enlarge and metastasize. As such, the advent of anti-angiogenic compounds has opened a new era of cancer treatment and the development of next-generation angiogenesis inhibitors remains a popular basis for chemotherapeutic drug design. Though a variety of pharmacologic agents have been engineered to target this process, an important discovery revealed that the ECM harbors an endogenous angiostatic factor in the class I small, leucine-rich proteoglycan, decorin [4]. Initial studies have demonstrated the ability of decorin to regulate collagen fibrillogenesis, thereby establishing a function for decorin in the preservation of the structural integrity of ECM [5–9]. Subsequent work has revealed that decorin plays a much more active role by regulating key cellular processes through its aptitude for binding to different receptor tyrosine kinases (RTKs) and modifying downstream signaling pathways [10–20]. In tumor cells, decorin acts primarily through the hepatocyte growth factor (HGF/Met) and epidermal growth factor receptor (EGFR) signaling axes to decrease the expression of the pro-angiogenic factors, vascular endothelial growth factor A (VEGFA) and hypoxia-inducible factor 1-α (HIF-1α), while simultaneously increasing the expression of thrombospondin-1 [11,21], a powerful anti-angiogenic protein [22], and tissue inhibitor of metalloproteinases-3 (TIMP3) [11,21], a key regulator of ECM turnover [11,21] (Fig. 1). The cumulative effect of these changes of the tumor secretome creates an anti-angiogenic and, subsequently less metastatic, tumor microenvironment.

Though decorin can alter the cellular milieu by controlling the secretion of angiogenic factors from tumor cells themselves, more recent work has uncovered a novel mechanism where decorin attenuates tumor progression by directly targeting the tumor microenvironment rather than acting solely on the tumor proper. A unique screen of orthologous tumor xenografts capable of differentiating between human and mouse gene expression revealed an increase in the tumor suppressor gene, paternally expressed gene 3 (*Peg3*), in decorin-treated animals compared to vehicle-treated controls [23]. Interestingly, this decorin-evoked gene induction occurs only in the tumor stroma and not in the tumor itself [23]. Given this information, a more detailed analysis of Peg3 expression in tumor-supporting cells upon decorin treatment revealed that Peg3 plays a role in mediating endothelial cell autophagy, the accumulation of cytoplasmic contents in double-membrane structures, which are eventually degraded via lysosomal machinery [24,25]. Mechanistically, decorin acts as a partial agonist for vascular endothelial growth factor receptor 2 (VEGFR2), the main receptor responsible for facilitating the angiogenic response in endothelial cells, resulting in a signaling cascade culminating in Peg3-dependent canonical autophagy involving the standard autophagic intermediates, Beclin 1 and microtubule-associated light chain protein 3 (LC3) [13,17] (Fig. 1). Decorin also competes with VEGFA, the canonical ligand of VEGFR2, to hinder angiogenesis [26]. As VEGFR2 is specifically expressed on endothelial cells, it is plausible that the anti-angiogenic property of decorin is linked to its induction of autophagy exclusively in the tumor vasculature. These findings are the first to link a soluble extracellular proteoglycan to the induction of the catabolic process of

autophagy and expose a novel function for matrix molecules to regulate the lysosomal degradation pathway.

Regarding the aforementioned decorin-mediated alteration of thrombospondin-1 secretion by tumor cells, it appears that thrombospondin-1 is surfacing as an important autophagic signaling molecule. For example, thrombospondin-1 inhibits RAS-positive tumor cell growth via autophagic induction [27]. On the contrary, studies blocking the function of CD47, the main thrombospondin-1 receptor, show a paradoxical increase in autophagic activity [28]. Thus, the ability of thrombospondin-1 to modulate autophagy appears to be quite complex, but may be important for putting together more pieces of the puzzle to understand better the ability of decorin to inhibit neovascularization.

Also of importance is the recent discovery that decorin is an autophagy-inducible proteoglycan [12,16] where nutrient deprivation and chemical inhibition of mammalian target of rapamycin (mTOR) signaling augment its expression both *in vitro* in fibroblasts as well as *in vivo* in cardiac tissue. In addition, *Dcn−/−* mice exhibit diminished cardiac autophagy vis-à-vis wild-type mice following a fasting challenge [12], validating the importance of decorin as a pivotal control center for the regulation of this catabolic process [16]. As pro-autophagic stimuli increase decorin expression, it is possible that the ability to modulate decorin levels in the tumor stroma may be a novel method for targeting neovascularization in the setting of cancer. Furthermore, in order to connect the processes of tumor progression and autophagy, a worthy hypothesis may be that, in the absence of decorin, lower levels of autophagy promote a pro-tumorigenic microenvironment.

In contrast, biglycan, another class I SLRP that shares the most structural homology with decorin [29,30], possesses pro-angiogenic properties through its ability to bind VEGFA and activate VEGFR2 signaling [31]. Additionally, when overexpressed in colon cancer cells, biglycan upregulates VEGFA leading to increased angiogenesis and tumor growth through activation of the extracellular signal-regulated kinase (ERK) pathway [32]. Therefore, the capacity to modulate angiogenesis appears to be specific to each respective proteoglycan, even within closely related members of the same family. Whether biglycan-mediated angiogenesis is related to autophagy remains to be seen. Interestingly, biglycan inhibits the angiostatic effects of endostatin [30]. As endostatin is a potent autophagic inducer in endothelial cells through the modulation of α5β1 integrin signaling culminating in increased Beclin 1 expression [30], it is possible that biglycan may inhibit autophagy by diminishing endostatin activity.

Like biglycan, perlecan, a large, basement membrane proteoglycan, exhibits pro-angiogenic properties [33–45]. Specifically, through its heparan sulfate side chains, the N-terminal domain I of perlecan sequesters and presents VEGFA and fibroblast growth factors (FGFs) to their respective receptors resulting in enhanced angiogenesis [46–51]. Importantly, mice that have been genetically designed without the heparan sulfate attachment site display diminished angiogenesis and compromised wound healing, presumably due to impairment in the juxtaposition of growth factors with their signaling receptors [52,53]. Along with its pro-angiogenic properties, perlecan also appears to be anti-autophagic as a recent notable discovery illustrates that conditional *Heparan sulfate proteoglycan 2−/−* (*Hspg2−/−)* mice

display enhanced autophagy in skeletal muscle [54] where they exhibit less mTOR activity than wild-type cohorts.

We note that perlecan is a multi-modular proteoglycan, where different domains serve different functions [55]. For example, while its N-terminal domain is pro-angiogenic, its C-terminal fragment, endorepellin, embraces properties very similar to those of decorin, where it is capable of restricting endothelial cell migration, capillary morphogenesis, and angiogenesis [35]. Indeed, previous studies demonstrate that endorepellin exclusively targets the tumor vasculature, resulting in decreased tumor growth [56]. In addition, endorepellin is able to initiate autophagy in endothelial cells utilizing a mechanism comparable to that of decorin, as both work through the Peg3-signaling axis to induce the pro-autophagic intermediates Beclin 1 and LC3 [57]. As both endorepellin and decorin exhibit the capability to induce autophagy as well as inhibit tumorigenesis through their actions in the tumor microenvironment, it is again likely that one mechanism by which this occurs is via suppression of angiogenesis through autophagic degradation of the vasculature. In fact, recent work suggests that the angiostatic mechanism of endorepellin is directly linked to autophagic induction [58]. Specifically, endorepellin inhibits vessel sprouting in *ex vivo* aortic ring assays, which can be blocked by inhibiting autophagy via the adenosine monophosphate kinase (AMPK) inhibitor, compound C [58]. Therefore, as decorin follows this same mechanistic paradigm, it is likely that it too reduces tumor neovascularization via an autophagic mechanism. Interestingly, endorepellin interacts with endostatin [35], the aforementioned potent pro-autophagic matrix protein. As this interaction diminishes endostatin's ability to reduce angiogenesis in endothelial cells, it may also prevent autophagic induction by either protein via a competitive binding mechanism.

Taken together, it appears that a distinct network is arising in the ECM that is important for the regulation of normal cell homeostasis as well as to counteract dysregulation of homeostasis in the tumor microenvironment. *In vivo*, it seems that there exist intricate feedback loops to allow for the induction and suppression of both autophagy and angiogenesis in response to environmental cues. Preliminary evidence for this stems from the observation that anti-angiogenic proteoglycans, like decorin [4], seem to be pro-autophagic and vice versa. As an aberration of either process can be detrimental to normal physiology, these pathways may become deregulated following some sort of insult or environmental stressor, leading to the onset of cancer. Continued deregulation may contribute to the progression of cancer and eventually to metastasis. As we continue to examine the signaling capabilities of these proteoglycans, we will gain a better perspective about the changes in the tumor microenvironment that lead to metastasis and how they are related to proteoglycan function or dysfunction. Furthermore, this knowledge will provide new management options for cancer where mimetics of endogenously occurring matrix components can be utilized for a safer, more efficacious treatment regimen than existing options.

Curtailing cancer progression: Targeting the tumor proper

Though we have focused mainly on detailing the actions of decorin and related proteoglycans in the tumor stroma, we must acknowledge that decorin, which is biologically

active as a monomer [59], also engages directly with the tumor proper via its interaction with a variety of RTKs abundant on the surface of different types of cancer cells [60–62]. One of the best-known decorin/RTK interactions is that between decorin and the EGFR resulting in p21-mediated cell cycle arrest, apoptosis, and diminished angiogenesis [63–65] (Fig. 1). Furthermore, decorin allows for EGFR to be degraded via caveolin-mediated endocytosis [66]. In addition, decorin antagonizes ErbB2/4 and platelet-derived growth factor (PDGF) signaling, both resulting in decreased tumor growth [67–69].

As described above, decorin interacts with the HGF/Met receptor to reduce angiogenesis by modifying the tumor secretome [70] (Fig. 1). In the tumor parenchyma, this same interaction results in an attenuation of β-catenin and Myc signaling, thereby directly inhibiting tumor growth [71] (Fig. 1). Notably, the decorin/Met interaction in triple-negative breast carcinoma cells evokes tumor cell mitophagy via the tumor suppressor, mitostatin [72] (Fig. 1). This decorin-evoked mitophagy likely comes as a consequence of mitochondrial depolarization and is the first documentation that decorin can regulate catabolism in cancer cells. Thus, it is likely that some of decorin's anti-tumorigenic activity comes through its interference with proper oxidative phosphorylation resulting in an energy imbalance in the setting of cancer. Furthermore, loss of mitostatin results in the inability of decorin to suppress VEGFA [72], coupling the ability of decorin to act simultaneously in the tumor microenvironment and the tumor proper.

Canonical autophagy in tumor cells in response to decorin stimulation has been recently reported in glioma cells, where decorin-mediated autophagic induction contributes to a reduction in cellular migration [73]. Though this is the first report of decorin-induced autophagy directly in cancer cells, it is likely that tumor cells that possess the proper receptors and subsequent signaling machinery also undergo autophagy in response to decorin treatment. For example, recent studies posit that inhibition of EGFR signaling results in autophagic induction [74]. As decorin is a potent ligand of EGFR, it is probable that tumor cells over-expressing this receptor, such as A431 squamous carcinoma cells or A549 lung carcinoma cells, respond with canonical autophagy instead of, or in concert with, mitophagy when challenged with decorin. Nevertheless, as our lab has demonstrated the necessity of Peg3 for decorin-mediated autophagy in endothelial cells, it would be unsurprising if decorin induces autophagy only in few tumor types as many cancers possess little to no endogenous Peg3 [75,76].

Again, despite being in the same family, biglycan takes on different functions in the context of tumor signaling. In fact, several tumor types, including colon and pancreatic cancer, express biglycan at higher levels than normal tissue substantiating the idea that biglycan is pro-tumorigenic as well as pro-angiogenic [77–79]. For instance, upregulation of biglycan in gastric cancer mechanistically promotes invasion and migration of these cells via phosphorylation and consequent activation of the focal adhesion kinase (FAK) signaling pathway [80]. In colon cancer cells, depletion of biglycan results in decreased proliferation and p21-mediated cell cycle arrest [32]. In addition, biglycan is capable of inhibiting apoptosis in these colon cancer cells by regulating p38 MAPK signaling [32]. Moreover, though its ability to augment Wnt/β-catenin signaling has only been explored in bone, some of the pro-tumorigenic effects of biglycan may also be attributed to its ability to amplify

Wnt/β-catenin signaling as well as its ability to interact with LDL-receptor related protein 6 (LRP6) [81]. Interestingly, autophagy attenuates Wnt-signaling, suggesting a potential link between biglycan and this catabolic process in cancer [82]. Also, though direct alterations of signaling pathways via biglycan are largely responsible for increased tumorigenesis, a secondary mechanism may be the ability of biglycan to modify the biophysical properties of the matrix itself. For example, as biglycan modifies FAK-signaling, it is likely that some of the increased invasiveness and tumor progression resulting from biglycan overexpression may come as a result of increased matrix stiffness, thereby facilitating the migration of cancer cells to increase metastasis.

Though the function of autophagy in cancer is controversial, it is emerging as an important therapeutic target. Whether it should be enhanced or inhibited appears to be context-dependent as in some cases autophagy is beneficial for reducing tumor growth and in others it seems necessary for cancer cell survival. Regardless, as both decorin and biglycan are major players in the inhibition and progression of tumorigenesis, parsing out the mechanism behind modulation of the autophagic pathway by them and other matrix constituents is critical for comprehending how to best fine-tune novel treatment strategies. Though the role of decorin in autophagy as it pertains to cancer is much more well-established than that of biglycan, it is very probable that biglycan will develop into a remarkable player in this signaling pathway in the future. Thus, we must focus our efforts on discovering more of the intricacies of these signaling regimes to hone our understanding of matrix regulation of tumor initiation and metastasis.

Complexity of biglycan signaling: Pro-inflammatory and danger signals

Besides its function as a structural molecule, the small leucine-rich proteoglycan biglycan can be either proteolytically released from the ECM upon tissue stress and injury or *de novo* synthesized by activated macrophages and resident cells [83]. In its soluble form, biglycan acts as a signaling molecule and endogenous ligand of the Toll-like receptors (TLR)-2 and -4 on the surface of macrophages. This biological interaction autonomously triggers sterile inflammation and potentiates pathogen-mediated inflammation via a second TLR that is not involved in pathogen sensing [83–85]. Mechanistically, by engaging TLR2 and TLR4, biglycan rapidly activates p38, ERK, and NF-κB signaling pathways. This leads to the synthesis and secretion of pro-inflammatory cytokines and chemokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, chemokine (C–C motif) ligand (CCL)2, chemokine (C-X-C motif) ligand (CXCL)1, CXCL-2, CXCL13, and CCL5 [83,84,86,87] (Fig. 2). This process initiates modulation of the immune environment and facilitates the recruitment of leukocytes to the site of inflammation.

The use of a transient transgenic mouse model in which biglycan is overexpressed in the liver under the albumin promoter and then released into the circulation has been instrumental for the deeper understanding of biglycan signaling *in vivo* [87]. This model has elucidated that soluble biglycan uses TLR2/4 signaling pathways, involving the adaptor molecule myeloid differentiation primary response 88 (MyD88), for the recruitment of neutrophils and macrophages while it regulates the infiltration of T cells exclusively through TLR4 and the

adaptor molecule TIR-domain-containing adapter-inducing interferon-β (TRIF) [87,88] (Fig. 2).

Moreover, biglycan organizes a multi-receptor crosstalk between TLR2/4 and the purinergic receptor, $P2X_7$ [85]. By clustering TLR2/4 and $P2X_7$, biglycan triggers the activation of caspase-1 through the NOD-like receptor protein 3 (NLRP3) inflammasome with subsequent release of mature IL-1β and IL-18 in a reactive oxygen species (ROS)- and heat shock protein (HSP)-90-dependent manner [85]. As a consequence, biglycan-deficient mice show improved survival in LPS-induced sepsis and less severe inflammation in both models of sterile inflammatory renal injury and LPS-induced sepsis, as monitored by decreased levels of active caspase-1 and therefore of mature IL-1β [83,85,89] (Fig. 2).

Thus, under pathological conditions soluble biglycan in its intact form, containing protein core and glycosaminoglycan (GAG) chain(s), and some biglycan fragments act as potent danger signals that mimic response to Gram-positive (via TLR2) and negative (via TLR4) pathogens [90]. While it is well established that the interaction of biglycan with TLR2 and the TLR4/MD2 complex occurs via protein core [83,84] the exact binding motifs are still under investigation. Interestingly, for the induction of TLR-dependent signaling the protein core of biglycan and at least one GAG side chain are required. Neither biglycan protein core nor GAG chains alone are capable of inducing TLR-dependent signaling and a proinflammatory response [83]. Therefore, it is conceivable that GAG chains of biglycan might be involved in the interaction with co-receptors and adaptor molecules of TLR2 and TLR4.

Proteolytic release of biglycan ensures a rapid inflammatory response to tissue stress or injury without the need for the *de novo* synthesis of biglycan. Several proteolytic enzymes such as bone morphogenetic protein-1 (BMP-1) [91], various matrix metalloproteinases (MMPs) [92] and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) and serine protease Granzyme B (GrB) have been shown to cleave biglycan. For details on biglycan degrading enzymes and cleavage of biglycan please refer to the recent review [93]. The fragments of biglycan acting as danger signals and proteinases involved in their generation are not identified yet. As biglycan protein core together with GAG side chain(s) trigger a proinflammatory response, it is tempting to speculate that not all of the generated biglycan fragments will be capable of binding to TLR2 and TLR4. Therefore, a proper inflammatory signal is secured by a very fast, *de novo* synthesis of biglycan in stimulated macrophages followed by additional synthesis in resident cells.

Biglycan tightly controls the severity of the inflammatory response

A novel mechanism has emerged wherein biglycan fine-tunes IL-1β production and restores immune homeostasis [89]. By using TLR2/4, biglycan triggers ROS generation in macrophages through NADPH oxidases (NOX) 1 and 4, thereby enhancing the expression and secretion of IL-1β. To impede this self-induced pro-inflammatory response, biglycan also triggers the synthesis and activation of NOX2 through selective TLR4 signaling pathways. While biglycan-mediated TLR4/TRIF signaling leads to the induction of *Nox2* mRNA expression, induction of TLR4/MyD88 signaling is required for activation of NOX2.

Activated NOX2 inhibits biglycan-mediated IL-1β synthesis [89]. It is tempting to speculate that these mechanisms of self-limiting inflammation are involved under physiological conditions to fine-tune IL-1β levels and could be therapeutically harnessed to treat inflammatory diseases.

However, there is strong evidence for beneficial effects of biglycan deficiency and pro-inflammatory effects of biglycan overexpression in various inflammatory diseases [93,94]. In fact, under pathological conditions biglycan stimulates the expression of HSP70 by selective utilization of TLR2. HSP70 binds to NOX2 thereby inducing its proteasomal degradation. This interaction consequently impairs the inhibitory function of NOX2 on IL-1β expression, promoting pro-inflammatory effects of biglycan (Fig. 2). Accordingly, in a mouse model of sterile renal inflammation, the lack of biglycan in *Nox2*-deficient mice is protective of hyperinflammation as well as massive macrophage infiltration, leading to less severe kidney damage [89].

Thus, these data describe how danger signals control the severity of the inflammatory response, by utilizing multi-receptor signaling, selective induction of TLR2 and TLR4 signaling pathways, adaptor molecules and downstream events such as ROS production. The discovery of the dual role of biglycan in inflammation will open new prospects for therapeutic intervention. It is likely that selective inhibition of biglycan-TLR2- or biglycan-TLR4 signaling could be a new therapeutic approach in inflammatory diseases. Alternatively, the stabilization of biglycan-mediated NOX2 expression or activation might represent a novel pharmacological avenue to overcome inflammation without interfering with physiological TLR signaling.

Biglycan stabilizes HIF-2α and evokes erythropoiesis

Recently, a novel function of biglycan has been discovered in a transgenic mouse model in which biglycan was constitutively overexpressed. Surprisingly, chronic increase in circulating biglycan leads to elevated hemoglobin concentrations, hematocrit values, and enhanced iron binding capacity, leading essentially to a clinical picture identical to secondary polycythemia [95]. Mechanistically, soluble biglycan induces polycythemia by triggering the hepatic and renal expression of erythropoietin (Epo), a key regulator of erythropoiesis. This occurs exclusively via TLR2 and involves biglycan-mediated stabilization of HIF-2α, most likely through a hypoxia-independent pathway [95].(Fig. 3). This information provides a new link for biglycan in the regulation of inflammation via stabilizing HIF-2α, a crucial trigger of pro-inflammatory cytokines, in macrophages [96]. Furthermore, these findings are in line with previous reports that biglycan selectively interacts with TLRs and their adapter molecules to achieve diverse biological outcomes [87,89]. While the clinical relevance of these findings has not been shown yet, it is conceivable that biglycan may critically impact tumorigenesis and cardiovascular disease by enhancing HIF-2α abundance and triggering secondary polycythemia.

Inflammatory biglycan signaling in tumor cell biology

Despite growing evidence for a relationship among innate immunity, inflammation, and tumor development, the mechanisms responsible for this association are not well-defined [97,98]. Although inflammation is a beneficial and essential mechanism in tissue injury and pathogen defense, it requires a rapid clearance of inflammatory cells [99]. Imbalance of inflammation resolution leads to infiltration of immune cells, which may generate large amounts of cytokines, chemokines, and ROS resulting in tissue damage and chronic inflammation, thus contributing to tumor initiation and progression [100]. Furthermore, the inflammatory microenvironment is considered a hallmark in each stage of tumor development [98].

Taking into account the intimate involvement of biglycan in inflammation, it is not surprising that the overexpression of biglycan is associated with a variety of human malignancies, such as pancreatic adenocarcinoma [101,102], colon cancer [102], ovarian cancer [103] intrahepatic cholangiocarcinoma [104], gastric cancer [80], esophageal squamous cell carcinoma [105], and melanoma [106]. Moreover, biglycan is involved as a regulator of tumorigenesis [60], a prognostic marker for cancer progression and survival [107], and a target for colon cancer diagnostics and treatment [108]. It is conceivable that biglycan triggers tumorigenesis directly via TLR2/4-NF-κB- and $P2X_7$-NLRP3-caspase-1-signaling or indirectly via downstream mediators such as pro-inflammatory cytokines, NOX enzymes, ROS, HIF-2α, Epo and VEGF [30,77,83,85,86,89,95] (Figs. 2 and 3). Indeed, there is mounting evidence that activation of TLR2 and TLR4 leads to cancer progression due to increased tumor cell proliferation, resistance to apoptosis, increased production of growth factors (e.g. TGF-β, VEGF) and of pro-inflammatory cytokines [109–111]. Downstream of TLR2/4, the adaptor molecule MyD88 and its oncogenically-active mutant forms, are considered mediators of tumorigenesis in various cancers [112]. Beyond that, there is no doubt that constitutive activation of NF-κB and MAPK pathways cause chronic inflammation which would favor cancer progression. The complex regulation of inflammation by biglycan is a result of signaling crosstalk between TLR2/4- and $P2X_7$-NLRP3-caspase-1-pathways [88,113,114]. While direct data on biglycan-NLRP3-caspase-1-signaling in carcinoma cells are not available yet, there is strong evidence for pro-tumorigenic effects of the NLRP3-caspase-1 signaling pathway [115,116]. Enhanced expression and activation of NLRP3 and caspase-1 is considered a poor prognostic sign for oncologic patients [115]. Therefore the development of inhibitors selectively targeting the NLRP3 inflammasome could be of potential therapeutic value.

Besides directly triggering pro-inflammatory TLR- and inflammasome-signaling, biglycan stimulates the generation of pro-inflammatory cytokines, NOX enzymes, ROS, HIF-2α, Epo and VEGF, which are crucial mediators of inflammation and angiogenesis in cancer development. Accordingly, enhanced generation of NOX-derived ROS in inflammatory tumors causes chromosomal DNA alteration and genomic instability, as well as induces tumor cell proliferation, survival, and metastasis [117,118]. Furthermore, enhanced HIF-2α, which might be due to biglycan-TLR2-dependent HIF-2α stabilization [95], has been detected in a variety of tumors with diverse histogenetic background [119,120]. Interestingly, there is growing evidence that generation of HIF-2α in cancer is restricted to

tumor-associated macrophages (TAMs) [119,121]. By regulating the expression of VEGF, VEGF receptors 1/2 and angiopoietins in TAMs, HIF-2α induces tumor angiogenesis and triggers the expression of genes involved in tumor cell proliferation and tumor invasion [122–124]. On the other hand, biglycan has been described to trigger endothelial cell migration and neovascularization of tumors due to its ability to induce VEGF synthesis in a TLR2/4-dependent manner [32,77,111]. Additionally, biglycan can generate a reservoir for VEGF, which in turn can be released during tumor-associated ECM-degradation, thus promoting angiogenesis [125]. Moreover, soluble biglycan is expressed in highly metastatic tumor endothelial cells, where it promotes tumor cell migration [126]. Thus, it is conceivable that during cancer development enhanced biglycan levels could promote stabilization of TAM-derived HIF-2α (Fig. 3) and trigger VEGF production and sequestration. Both bioactivities would ultimately trigger tumor angiogenesis.

During tumorigenesis a cross-talk between tumor and stromal cells modifies the microenvironment and the ECM [127]. The expression of biglycan by stromal fibroblasts is induced by TGF-β, a multi-purpose growth factor [128,129] which might then use the TLR2/4 on stromal macrophages to further modulate the tumor microenvironment and to induce the recruitment of tumor cells through chemokine production. In addition, biglycan is able to increase the affinity of TGF-β to its receptor and therefore promote cancer progression. Thus, we presume, that biglycan-triggered TGF-β signaling might create an environment, which is prone to tumor development, by triggering the expression of matrix proteins and enzymes involved in matrix remodeling [130,131]. Moreover, TGF-β activates fibroblast-to-myofibroblast differentiation [132,133], as well as epithelial-to-mesenchymal transition (EMT) [134] thus increasing the potential for metastasis. Furthermore, decorin interacts with TGF-β [62], to inhibit its signaling pathway, resulting in the reduction of fibrosis [135]. Interestingly, TGF-β inhibits decorin transcription [136], a finding opposite to the TGF-β-mediated induction of biglycan. These disparate functions of decorin and biglycan in the context of TGF-β signaling solidify the contrasting effects seen on tumorigenesis by these related proteoglycans, where one diminishes tumor progression while the other promotes disease.

Enhanced Epo production based on biglycan-TLR2-HIF-2α signaling [95] provides an additional indirect mechanism of biglycan promoted tumorigenesis. Upon binding to erythropoietin receptors present on carcinoma cells, Epo promotes tumor growth, local invasion, metastasis, angiogenesis and lymphangiogenesis [137–140] (Fig. 3). Thus, there is a plethora of direct and indirect mechanisms through which biglycan promotes inflammation and angiogenesis resulting in tumor progression.

Besides strong indications for pro-oncogenic functions of biglycan, there are also some reports describing tumor suppressive effects of biglycan. For example, biglycan induces cell growth arrest in pancreatic cancer cell lines *in vitro* [78] and inhibits bladder cancer cell proliferation [141]. Interestingly, although elevated levels of biglycan correlate with high-grade human bladder cancer and muscle invasiveness, enhanced expression of tumor-associated biglycan is linked to a better survival rate [141]. Accordingly, knockdown of biglycan leads to increased proliferation of bladder cancer cells, indicating biglycan as an endogenous inhibitor of cancer cell growth in urothelial neoplasms [141]. In addition,

biglycan induces a high intratumoral inflammatory reaction as well as an enhanced autologous tumor response in diffuse large B-cell lymphomas, leading to improved therapeutic outcome and survival [142]. Presumably, this dual role of biglycan in tumorigenesis depends on the tumor cell type and differentiation stage (Fig. 2). According to our current knowledge, a biglycan-mediated chronic inflammatory milieu should promote tumor growth. However, acute inflammation caused by administration of biglycan into established tumors actually reduces malignant growth, analogous to beneficial effects of decorin-TLR2/4 signaling [143] (Fig. 2).

Taken together, the multifunctional involvement of biglycan in the regulation of inflammation makes it a potentially druggable target for cancer remedies as well as a novel anti-oncogenic therapeutic agent on its own.

Pro-inflammatory signaling of decorin

Analogous to biglycan, decorin induces a TLR2/4-dependent signaling cascade in macrophages leading to the activation of the MAPK, ERK, stress-activated protein kinase (SAPK) and p38 signaling pathways, and subsequently to the synthesis and secretion of CCL-2, TNF-α and IL-12p70 [143,144]. Moreover, decorin possesses the ability to further drive the cytokine profile toward a pro-inflammatory phenotype by impeding the production of the anti-inflammatory cytokine, IL-10, by macrophages. By sequestering active TGF-β, decorin reduces the abundance of TGF-β-driven oncogenic microRNA (miR)-21. miR-21 is a translational inhibitor of the tumor suppressor programmed cell death protein 4 (PDCD4), which itself post-translationally suppresses IL-10. Consequently, increased PDCD4 production causes reduction of IL-10 protein abundance [143]. Indeed, due to creating an inflammatory milieu in the tumor microenvironment together with reduction of the oncogene miR-21 and enhancement of the tumor suppressor PDCD4, decorin inhibits growth of established tumors [143]. Thus, decorin, as an important modulator of malignant growth, metastasis and tumor microenvironment [67,68,145–148] might be a useful tool for anti-tumor interventions.

Conclusions and perspectives

The functions of decorin in tumor biology continue to surface as more sophisticated research tools become available [149,150]. Though decorin has been touted as a “guardian from the matrix” for many years, this designation was primarily given due to its ability to alter RTK-signaling, resulting in reduction of tumor growth via cell cycle arrest. More recent work demonstrates the incredible versatility of this SLRP as decorin has now acquired a new role as a potent autophagic inducer in endothelial cells and a pro-mitophagic agent in tumor cells. The ability for decorin to regulate these signaling pathways offers a new perspective on matrix-regulation of both the tumor microenvironment as well as the tumor proper. Specifically, the capacity of decorin to both inhibit angiogenesis as well as act directly on the tumor proper makes it an ideal candidate for drug design. Furthermore, as decorin is a naturally-occurring proteoglycan, the side effects of using purified decorin or its biologically active fragments will likely be minimal, making it an attractive option for chemotherapy.

Moving to biglycan, research of the last two years has exponentially improved our knowledge regarding the role of this SLRP in inflammation and angiogenesis. There is now evidence that, besides mediating inflammation by biglycan, TLR2/4 are required for biglycan-dependent synthesis of VEGF and, therefore, regulation of angiogenesis. Furthermore, it became clear that biglycan is not only a pro-inflammatory stimulus but is also capable of self-limiting inflammation. The underlying mechanism of how biglycan tightly balances pro- and anti-inflammatory responses under physiological conditions has been provided [89]. Hopefully, these data will encourage further research on the mechanisms regarding anti-inflammatory signaling of other ECM-derived danger signals.

Beyond the well-known biglycan-dependent orchestration of various receptor signaling, another level of complexity in biglycan-dependent regulation of inflammation has recently been described [89]. It is now obvious that besides common signaling via TLR2 and TLR4, biglycan selectively binds to only one TLR. After choosing the receptor, the next step of signaling is achieved at the level of TLR adaptor molecules, finally resulting in a very specific downstream outcome. This might explain why, in certain cell types and under certain conditions, biglycan could actually suppress tumorigenesis. The mechanisms of how this selection of receptors and adaptors is regulated are not known yet. It is conceivable, however, that various co-receptors might help biglycan to “make that specific choice”.

One example for a specific outcome of biglycan-TLR2 signaling is the newly-identified function of biglycan to stabilize HIF-2α and increase Epo production [95]. The exact mechanisms for biglycan-mediated HIF-2α stabilization still need to be elucidated. Although little is known about the biglycan-HIF-2α-Epo signaling axis during tumorigenesis, it is likely that the blockade of biglycan/TLR2-binding could protect against malignant growth. However, given that TLRs have crucial physiological functions, future studies are essential to unravel co-receptors and downstream mechanisms of biglycan/TLR-signaling for selective druggability in the context of cancer.

In conclusion, both decorin and biglycan are important mediators of tumor initiation and progression involving the cellular pathways of angiogenesis, inflammation, and autophagy. As the tumor microenvironment is a complex amalgam of different cell types and signaling molecules, it is probable that these critical cellular processes are intertwined in an intricate system to alter cell growth, metastasis, and nutrient availability for both normal and cancer cells. Therefore, it is important to focus on these pathways and their regulation by these and other matrix constituents in order to gain a closer understanding of the timeline of events involved in tumor initiation as well as to define which pathways are deregulated leading to tumor progression. Future therapeutic modalities will materialize as the nuances of these signaling pathways are elucidated, and thus it is essential to continue our efforts of unravelling the role of these proteoglycans in normal and aberrant physiology.

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Abbreviations

AMPK	adenosine monophosphate kinase
CCL	chemokine (C–C motif) ligand
CS/DS	chondroitin sulfate/dermatan sulfate
CXCL	chemokine (C-X-C motif) ligand
ECM	ECM
EGFR	epidermal growth factor receptor
Epo	erythropoietin
ERK	extracellular signal-regulated kinases
GAG	glycosaminoglycan
HGF/Met	hepatocyte growth factor
HIF	hypoxia inducible factor
HSP	heat shock protein
HSPG2	heparan sulfate proteoglycan 2
IL	interleukin
LC3	microtubule-associated protein light chain 3
LRP6	LDL-receptor related protein 6
MyD88	Myeloid differentiation primary response protein
NOX	NADPH oxidase
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3	NOD-like receptor protein 3
PDGF	platelet-derived growth factor
Peg3	paternally expressed gene 3
ROS	reactive oxygen species
SLRP	small, leucine-rich proteoglycan
TAM	tumor associated macrophages
TLR	Toll-like receptor
TGF-β	transforming growth factor β
TRIF	Toll/IL-1R domain-containing adaptor inducing IFN-β

VEGF vascular endothelial growth factor

VEGFR2 vascular endothelial growth factor receptor 2

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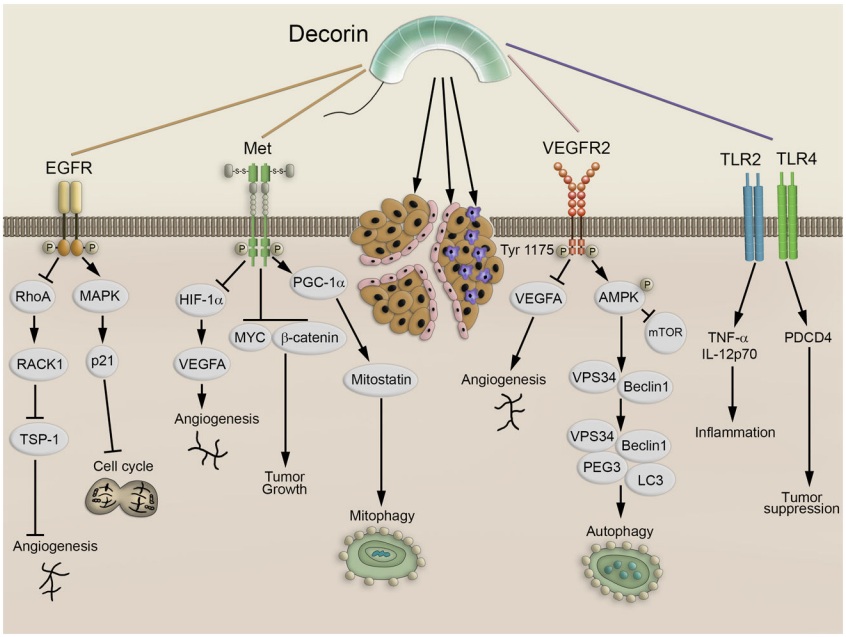

Fig. 1.

Decorin exhibits promiscuity in its ability to alter tumorigenesis via regulation of angiogenesis, autophagy, and inflammation. Decorin antagonizes RTKs, such as EGFR and Met, on the tumor cell surface to inhibit angiogenesis via suppression of pro-angiogenic factors, such as VEGFA, as well as induction of anti-angiogenic proteins, such as thrombospondin-1, while simultaneously reducing tumor growth via cell cycle arrest and inhibition of Myc and β-catenin. Signaling through Met also induces mitostatin leading to tumor cell mitophagy. Interaction between decorin and VEGFR2 in endothelial cells results in autophagic induction vis-à-vis the canonical intermediates, Beclin 1 and LC3 as well as with the novel autophagic regulator, Peg3. In inflammatory cells, decorin signals through TLR2/4 to induce pro-inflammatory mediators, which reduces tumor growth.

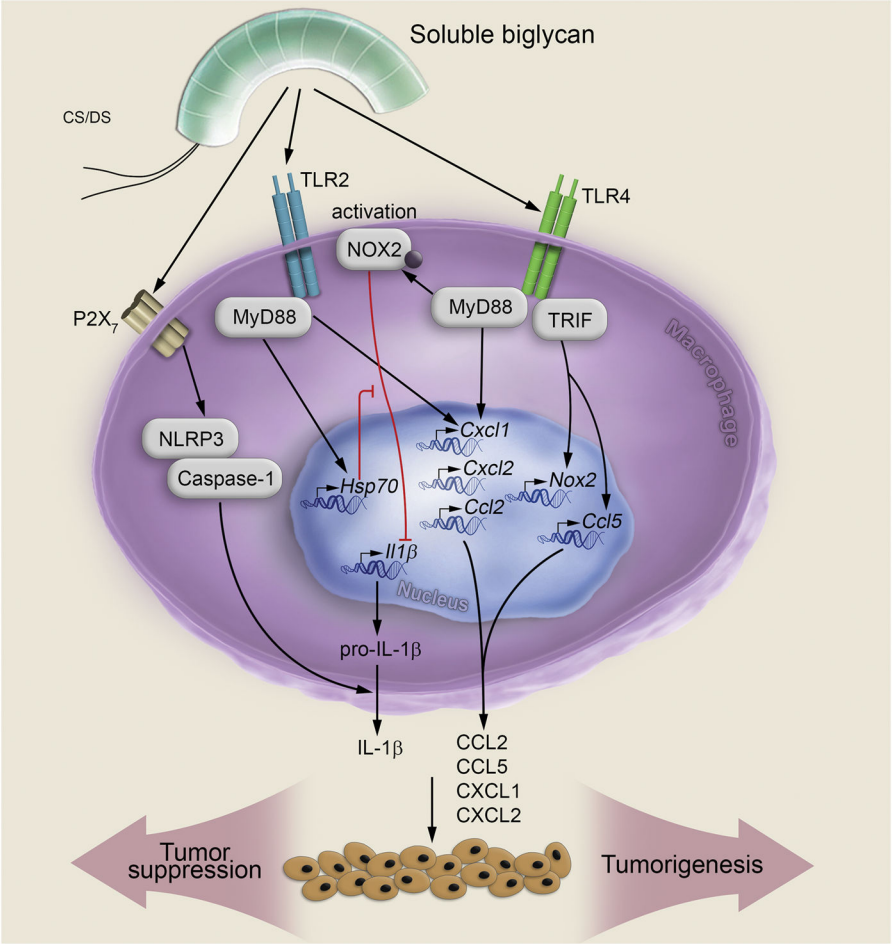

Fig. 2.

Dual role of biglycan in the control of inflammation and tumorigenesis. Soluble biglycan triggers mRNA expression of pro-inflammatory cytokines and chemokines Il1β, Cxcl1, Cxcl2, and Ccl2 in macrophages in a TLR2/4- and MyD88-dependent manner, while it selectively stimulates the expression of Ccl5 through TLR4 and TRIF. By clustering TLR2/4 and the $P2X_7$ soluble biglycan induces the NLRP3-inflammasome, activating caspase-1 and releasing mature IL-1β. Moreover, biglycan directly mediates the expression of Nox2 mRNA via TLR4/TRIF and the activation of NOX2 in a TLR4/MyD88-dependent manner, thereby attenuating the expression of the pro-inflammatory cytokine IL-1β. In contrast, by engaging TLR2, soluble biglycan triggers the expression of HSP70, which binds to NOX2, and consequently impairs the inhibitory function of NOX2 on biglycan-mediated IL-1β expression and maturation.

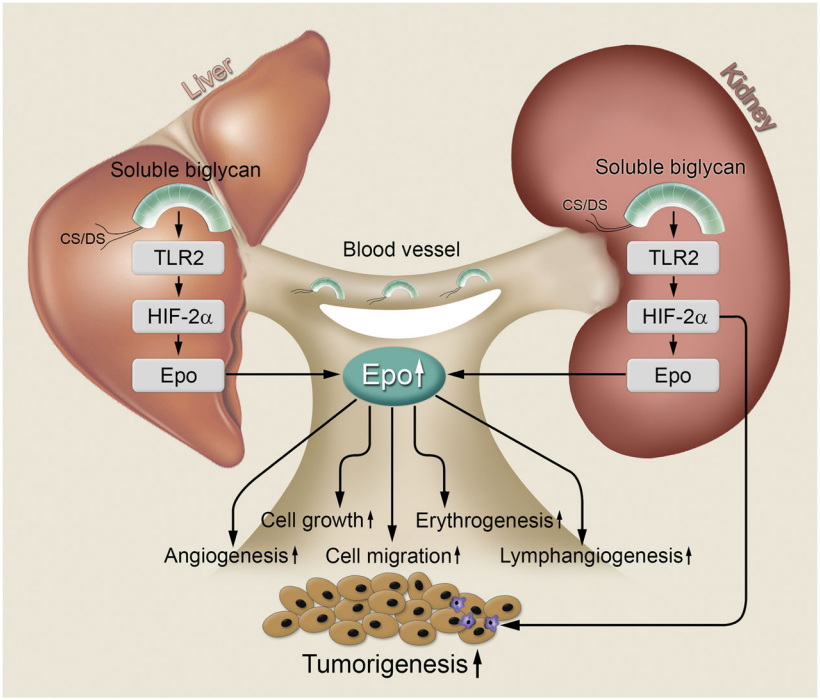

Fig. 3.

Biglycan induces tumorigenesis via HIF-2α stabilization and Epo expression. Soluble biglycan binds to the TLR2 in the kidney and/or in the liver and induces the stabilization of HIF-2α produced in liver, kidneys and tumor-associated macrophages (purple). HIF-2α subsequently induces the expression of erythropoietin (Epo). Epo is than released into the circulation, where it may stimulate tumor angiogenesis, cell growth and cell migration, as well as tumor lymphangiogenesis, thus inducing tumorigenesis.