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Decoding the Matrix: Instructive Roles of Proteoglycan Receptors

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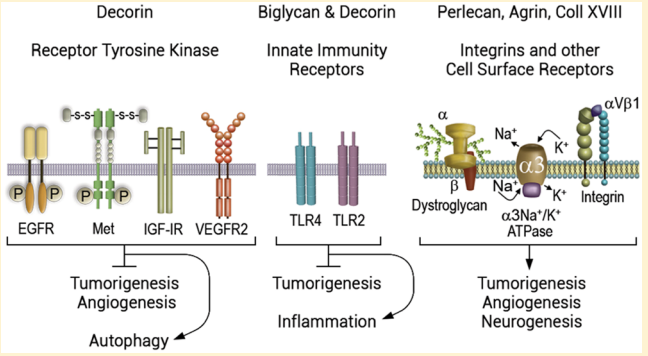
ABSTRACT: The extracellular matrix is a dynamic repository harboring instructive cues that embody substantial regulatory dominance over many evolutionarily conserved intracellular activities, including proliferation, apoptosis, migration, motility, and autophagy. The matrix also coordinates and parses hierarchical information, such as angiogenesis, tumorigenesis, and immunological responses, typically providing the critical determinants driving each outcome. We provide the first comprehensive review focused on proteoglycan receptors, that is, signaling transmembrane proteins that use secreted proteoglycans as ligands, in addition to their natural ligands. The majority of these receptors belong to an exclusive subset of receptor tyrosine kinases and assorted cell surface receptors that specifically bind, transduce, and modulate fundamental cellular processes following interactions with proteoglycans. The class of small leucine-rich proteoglycans is the most studied so far and constitutes the best understood example of proteoglycan−receptor interactions. Decorin and biglycan evoke autophagy and immunological responses that deter, suppress, or exacerbate pathological conditions such as tumorigenesis, angiogenesis, and chronic inflammatory disease. Basement membrane-associated heparan sulfate proteoglycans (perlecan, agrin, and collagen XVIII) represent a unique cohort and provide proteolytically cleaved bioactive fragments for modulating cellular behavior. The receptors that bind the genuinely multifactorial and multivalent proteoglycans represent a nexus in understanding basic biological pathways and open new avenues for therapeutic and pharmacological intervention.



Instructive cues fundamental for all aspects of multicellular life reside within the ubiquitous and evolutionarily conserved extracellular matrix (ECM). These functional signals range from fully embedded solid phase ligands to soluble mediators that function in a paracrine and/or autocrine fashion by engaging in high-affinity interactions with cell surface receptors.[1−6] Integrating and parsing bidirectional inputs and outputs allow the ECM to reign as a key regulator for maintaining optimal cell and tissue homeostasis.[7,8] Cells interpret and process this dynamic repository of information through various supramolecular signaling complexes, including RTKs, innate immune receptors, and integrins.[6,9]

The prominent subclasses of matrix constituents responsible for instructive signal transduction include the diverse and multifaceted small leucine-rich proteoglycan (SLRP) gene family and several members of the pericellular heparan sulfate proteoglycans that reside within basement membranes.[8,10] The original discovery that soluble, monomeric decorin[11] is capable of binding EGFR and communicating with the intracellular signaling apparatus via cell surface signaling receptors[12] pioneered the paradigm-changing concept that matrix components embody a critical regulatory network.[5,13−17] Following this initial discovery, decorin emerged as the leading candidate for a matrix-derived repressor of tumorigenic growth with inherent angiostatic and pro-autophagic activities[18−20] that wholly manifests from RTK partial agonism. The repertoire of functions ascribed to decorin has since expanded exponentially and now participates in a plethora of diverse processes such as fibrillogenesis and wound healing,[21−23] keratinocyte function,[24] allergen-induced asthma,[25] delayed hypersensitivity,[26] diabetic nephropathies and renal diseases,[27,28] skeletal muscle homeostasis,[29] nurturing hematopoietic stem/progenitor cell niches,[30] and ensuring proper convergent extension.[31]

Biglycan, a member of the class I SLRP family that is most homologous to decorin, has also been involved in receptor engagement and coordination of intracellular signaling pathways. For example, both circulating biglycan and decorin have been implicated in regulating innate inflammatory responses downstream of TLR2/4 (see below).[5,9,32−34] Decorin and biglycan also share overlapping functions in the mechanobiology of tendon structure[35−37] and have distinct roles in fetal membrane signaling.[38] Further, the control of cellular phenotype via ligation of distinct signaling receptors has also been attributed to molecules associated with basement membranes such as perlecan, agrin, and collagen XVIII.[39] Moreover, some of the basement membrane HSPGs (perlecan

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and collagen XVIII) are proteolytically processed to liberate a soluble, bioactive fragment capable of engaging cognate receptors.[40,41]

Although proteoglycans have been previously shown to play a role as endocytic receptors,[42−44] in this Current Topic, we will evaluate a unique class of signaling receptors that engage and transduce proteoglycan-derived cues. These activities can profoundly impact and reprogram the central processing and integration networks responsible for cell behavior, phenotype, and the development of various pathologies. Therefore, we will critically evaluate the pathways downstream of proteoglycan receptor engagement relevant for tumorigenesis, angiogenesis, autophagy, and immunomodulation.

DECORIN ENGAGES A MULTITUDE OF RTKS FOR PROTRACTED TUMORIGENIC SUPPRESSION

Decorin has emerged as a soluble pan-RTK inhibitor. However, decorin was initially discovered and characterized as a putative collagen-binding factor active in competent collagen synthesis, assembly, deposition, and fibrillogenesis.[37,45−48] Decorin also binds multiple matrix components necessary for structural integrity[14] and sequesters pleiotropic growth factors, with a predominant tendency to inactivate several TGF-β family members,[14,18] which consequently suppress downstream TGF-β signaling in an indirect fashion.[14,18] One receptor-dependent mechanism of TGF-β regulation involves decorin-mediated engagement of the endocytic receptor, lipoprotein receptor-related protein 1 (LRP-1),[49] resulting in PI3K activation and TGF-β modulation via trimeric Smad signaling. Famously and primarily, decorin is a soluble tumor repressor that neutralizes tumorigenic growth and unchecked neovascularization, vis-à-vis RTK-mediated pro-autophagic signaling pathways.[19] For this reason, decorin has been appropriately designated as "a guardian from the matrix".[14] Importantly, the well-established antitumorigenic and anti-angiogenic properties borne from the interaction of decorin and receptor (as discussed below) are independent of the covalently attached chondroitin/dermatan sulfate glycosaminoglycan chain.[50−52] Therefore, this review will focus exclusively on signaling events and cellular responses as mediated by the respective proteoglycan core protein.

EGFR AND MET: IT STARTED WITH A TALE OF TWO RECEPTORS

The epidermal growth factor receptor (EGFR) was the original RTK discovered that binds decorin with high affinity[12] (Figure 1). Following stimulation of A431 cells, decorin promotes EGFR receptor dimerization, rapid trans-autophosphorylation of the unstructured intracellular tails, and increased cytosolic calcium levels[53] and evokes EGFR internalization in caveolin-1 positive endosomes.[14] Presumably, following clearance of the receptor from the tumor cell surface, the ternary decorin/EGFR/caveolin-1 complex traffics and ultimately fuses with the lysosomal compartment for receptor complex degradation concomitant with a cessation of EGFR signaling.[54] Intriguingly, the ligand-binding site of decorin on EGFR partially overlaps with that of EGF, as decorin significantly competes off bound EGF.[55] Despite this narrow binding cleft shared by EGF and decorin, biologically distinct phenotypes occur insofar as receptor stability, signal intensity, and signal duration. Indeed, EGF sustains the maximal phosphorylation state and signaling capacity of postinternalized EGF:EGFR complexes and permits additional waves of signaling (e.g., bound MAPK, PI3K, and

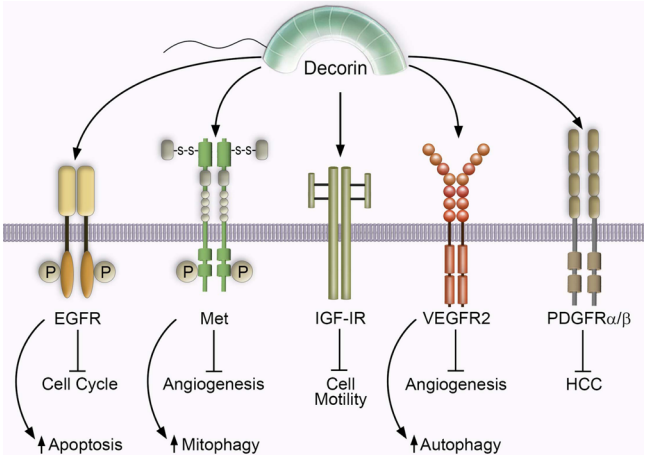

Figure 1. Decorin interacts with several receptor tyrosine kinases for the control of fundamental cellular behaviors in normal and malignant circumstances. Schematic representation of cell surface receptor tyrosine kinases occupied by decorin. Biological consequences of binding and resultant signal transduction are outlined below the appropriate receptor. Please see the text for additional information.

PLC-γ1 components) followed by sorting into an endosomal recycling pathway that repopulates the cell surface with active EGFR.[56] In contrast, after evoking a brief burst of EGFR phosphorylation, declining EGFR cell surface levels (>50% of total), and transient activation of MAPK (ERK1/2), decorin exerts a protracted attenuation of downstream signaling effectors that paradoxically results in cell cycle arrest (induction of the cyclin-dependent kinase inhibitor, $p21^{WAF1}$) and caspase-3-mediated apoptosis (Figure 1).[4,57] Interestingly, depending on the phosphorylation signature decorin evokes, phosphorylated EGFR associates with caveolin-1-coated pits.[58] Unsurprisingly, EGFR is not the only Erb family member by which decorin serves as a direct soluble repressor as ErbB4 is targeted by decorin during scar tissue repair in the central nervous system.[59]

A recurring hallmark of decorin binding served as the utilitarian means for the identification of Met (known as hepatocyte growth factor or scatter factor receptor) as the primary RTK by which decorin transduces biological information[7,60] (Figure 1). In analogy with EGFR, decorin evoked a rapid but transient burst at a phosphotyrosine residue that can be detected via a targeted phosphotyrosine RTK array platform.[60] Moreover, Met was characterized as the central RTK for decorin-mediated antitumorigenicity and angiostatic properties[50,52,60] vis-à-vis higher-affinity binding for Met[60] as well as via biological, pharmacological, and genetic methodologies.[52,60] Binary decorin/Met complexes avidly colocalize with caveolin-1 positive endosomes (for proficient lysosomal degradation), whereas pro-tumorigenic HGF/Met complexes associate with clathrin for receptor recycling and additional cycles of signaling.[50] Consequentially, two potent effector oncogenes downstream of Met signaling, β-catenin and Myc, are targeted for protracted degradation via the 26S proteasome.[14,50,61] Mechanistically, degradation of Myc—following phosphorylation at Thr58, which is situated within an established degron—permits *CDKN1A* derepression via loss of the AP4 transcriptional repressor.[50] Moreover, decorin utilizes Met as the nexus for angiogenic suppression[52] in HeLa and MDA-MB-231 cells (Figure 1). Signaling positively through Met, decorin noncanonically suppresses *HIF1*

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expression via transcriptional repression. Compromising HIF-1α expression subsequently decreases the level of expression of VEGFA and MMP2/9 with a concurrent increase in the level of puissant anti-angiogenic effectors such as thrombospondin-1 (TSP-1) (see below) and TIMP-3.[14,18,52] Collectively, decorin subverts the pro-angiogenic signaling network via prolonged attenuation of Met in neoplastic cells.

Similar binding mechanics notwithstanding, decorin may integrate signaling among multiple RTKs expressed by a single cell via the empirically determined binding constants of each receptor, the prevailing density of the receptor, and the uniform inclusion of specific structural motifs (e.g., the IgG domain). Moreover, decorin may functionally titrate total receptor levels (via degradation) and thereby deprive signaling clusters of key receptors necessary for competent signal transduction for the development and progression of cancer. This biological process has already been observed via the physical sequestration of EGFR from EGFR/ErbB1:Her2/Neu/ErbB2 heterodimers.[7,14] A pertinent example of differential signal integration is the rapid release of TSP-1 from basal breast carcinoma cells[62] in a RhoA/ROCK1-dependent manner. Although MDA-MB-231 cells constitutively express EGFR and Met, pharmacological inhibition and RNAi-mediated silencing of Met did not perturb decorin-induced TSP-1 secretion whereas blocking EGFR completely abrogated this effect[62] (Figure 1). Functionally, differences may reside in the phosphorylation signatures of the flexible intracellular tails flanking the kinase domain or in the geometrically constrained structural conformations the receptors adopt following decorin binding.

Recently, a novel mechanism in which decorin, acting as a partial Met agonist, induces tumor cell mitophagy (mitochondrial autophagy) has emerged as the molecular basis for the observed angiostatic effects in basal breast carcinoma.[18,19,63] Mitophagic induction may be a general phenomenon as it also occurs in prostate carcinomas transduced with decorin-expressing adenovirus.[61] Induction of tumor cell mitophagy is entirely dependent on the complex interaction between PGC-1α and mitostatin.[19,63] Loss of mitostatin, a putative tumor suppressor gene,[64,65] via RNAi silencing prevents mitophagy and significantly compromises VEGFA suppression following the administration of decorin[63] (Figure 1). Thus, decorin can negatively regulate two RTKs, EGFR and Met, potent drivers of cancer and angiogenesis, and this influence could be due to an endogenous, stromally derived force to restrain cancer growth and infiltration.

INSULIN-LIKE GROWTH FACTOR RECEPTOR 1 (IGF-IR): THE DECORIN DUALITY

The role of environmental and context-specific signaling is further illustrated with the interaction between decorin and IGF-IR.[66] An intriguing duality between normal, genomically stable cells (e.g., endothelial cells)[67] and tumor cells (e.g., bladder carcinoma)[68] emerges following decorin engagement of IGF-IR (Figure 1). In endothelial cells, decorin triggers levels of IGF-IR phosphorylation comparable to that evoked by IGF-I coincident with downstream Akt signaling via the N-terminus of decorin.[66,68] Further, decorin is capable of stimulating endothelial cell adhesion and migration of endothelial cells over fibrillar collagen networks in an IGF-IR/$\alpha2\beta1$ integrin-dependent manner upstream of Rac activation.[69] Decorin also regulates renal fibrosis by directly engaging IGF-IR present on renal fibroblasts and indirectly by inhibiting the biological activity of CTGF (CCN2).[70,71] Moreover, decorin promotes the PI3K/Akt/mTOR pathway in renal cells, which indirectly promotes fibrillin-1 translation, thereby curbing TGF-β bioavailability.[72−74] Substantially antithetic to the aforementioned role of decorin as a pan-RTK inhibitor, decorin can be a full IGF-IR agonist, analogous to IGF-I, in genomically stable cells. In this case, soluble decorin exerts positive IGF-IR phosphorylation consistent with improved receptor stabilization and robust downstream effector activity under physiologically relevant conditions.[66] In contrast, the net output of IGF-I/IGF-IR signaling in a neoplastic setting promotes urothelial tumor cell motility via Akt/MAPK-dependent paxillin activation,[75] where decorin can bind IGF-I and associated IR-A ligands[76] and the IGF-IR in a region that does not overlap with the IGF-I-binding domain.[68] Orthodox paradigms regarding the interaction of decorin with cognate receptors no longer apply when discussing the effect of decorin/IGF-IR complexes in a tumorigenic setting.[66,68] Decorin does not compromise or enhance the IGF-IR phosphorylation state upon binding but allosterically competes and suppresses IGF-I-mediated activation of IGF-IR and downstream Akt/MAPK pathways.[68] Moreover, prolonged stimulation by decorin neither perturbs receptor stability nor triggers internalization of the receptor complex with caveolin-1, unlike EGFR and Met, but does trigger degradation of IRS-1.[68] This decorin/IGF-IR interaction is the only known instance whereby decorin does not cause RTK internalization and association with caveosomes. Decorin-evoked negative regulation of IGF-IR culminates in decreased IRS-1 stability that will ultimately prove to be insufficient for sustainable Akt/MAPK (and paxillin) activity, thereby abrogating IGF-I-induced tumor cell motility (Figure 1). It was recently discovered that IGF-I requires a novel kinase involved in urothelial cell motility known as Pyk2.[77] It remains unknown whether Pyk2 is downstream of IGF-IR/IRS-1/Akt/MAPK signaling and whether decorin inactivates this kinase for motility termination. Thus, decorin can exert opposite effects on the IGF-IR system, and these effects are dependent on the cell context.

VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR 2 (VEGFR2): A NEW ERA FOR SLRPS

A unique high-resolution transcriptomic platform capable of differentiating species-specific transcripts from engrafted *Homo sapiens* orthotopic tumors (MDA-MB-231) from the recipient *Mus musculus* microenvironment has changed our understanding of decorin (and thus SLRP) biology.[51] These analyses revealed an exclusive subset of genes that are differentially regulated only within the tumor stroma. Among these genes, *Peg3* emerged as a highly favored candidate.[51] Utilizing endothelial cells (MDEC and HUVEC) as a proxy for the mouse tumor stroma, we found that Peg3 was intimately involved in orchestrating decorin-evoked endothelial cell autophagy[18−20,78] under nutrient-enriched conditions. Further analysis revealed a strict dependence on the primary endothelial cell RTK, VEGFR2, as the mechanism for decorin-mediated autophagy and angiostasis[78] (Figure 1). In a similar mechanism, decorin bioactivity requires competent RTK signaling as inhibition of VEGFR2 with the small molecule inhibitor SU5416 or genetic depletion of the receptor abrogates Peg3 induction and subsequently prevents an increase in the levels of Beclin 1 and LC3.[78] Therefore, decorin acts as a partial VEGFR2 agonist, whose predicted ligand-binding domain partially overlaps with that of VEGFA, the natural ligand of VEGFR2.[20,78] Proficient autophagic stimulation relies on

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decorin/VEGFR2 interactions and subsequent downstream AMPKα activation (at Thr172).[19,79,80] Critically, AMPKα serves as the chief energy-sensing kinase responsible for autophagic initiation by inhibiting the anti-autophagic mTOR pathway.[81] This represents the first report that AMPKα can be activated by an upstream RTK and that it is stimulated in a manner commensurate with canonical autophagic stimuli (e.g., amino acid withdrawal and nutrient deprivation, rapamycin, or Torin-1).[79] Moreover, the magnitude of autophagic induction attained with decorin is comparable to traditional methods of inducing autophagy. Therefore, decorin can be considered a soluble pro-autophagic effector that requires and binds two distinct pro-autophagic receptors, i.e., Met for tumor cell mitophagy and VEGFR2 for endothelial cell autophagy. In both instances, their tyrosine kinase activity is necessary for downstream biological function.

PLATELET-DERIVED GROWTH FACTOR RECEPTOR (PDGFR): DECORIN IS A GENUINE PAN-RTK INHIBITOR

A prime example of the pervasive and widespread effect of decorin-mediated RTK antagonism lies with the identification of platelet-derived growth factor receptor α/β (PDGFR α/β) as a key target for combatting tumorigenesis.[82] Utilization of two different chemically induced models of hepatocellular carcinoma (HCC) in either a wild-type or *Dcn*$^{-/-}$ background,[82] has identified several RTK targets. The screen revealed that when decorin is globally deleted, many RTKs become hyperactive, i.e., an increase in the magnitude of the phospho-Tyr signal, even under basal conditions.[82] From this screen, PDGFR α/β has emerged as a high-affinity interacting partner for decorin and proved to be a critical avenue by which decorin suppresses HCC development and progression[82,83] (Figure 1). Thus, a genetic background lacking an important signaling SLRP causes a constitutive activation of several RTKs, a function not attributable to the collagen binding role of decorin during development and tissue homeostasis.[84] The constitutive activation of RTKs in the absence of decorin, thus, provides a mechanistic explanation for a permissive role of decorin in tumorigenesis as shown in other genetic cancer models.[85−87]

INCITING INFLAMMATION

A second, closely related class I SLRP, biglycan, is more than 65% homologous with decorin in both human and mouse genes.[6,8] Biglycan contains two covalently attached glycosaminoglycan chains, hence earning the eponym of biglycan.[6] Functionally, biglycan sequesters and modulates the activity of several TGF-β superfamily members, including TGFβ/Smad2[88,89] and BMP-4.[90] In addition, biglycan modulates the Wnt/β-catenin signaling axis[91] (see below). Biglycan also binds and potentiates VEGFA signaling during fracture healing under normal physiological conditions.[92] Indeed, decorin may also be pro-angiogenic in certain physiological settings.[14] Nonoverlapping functions do exist between biglycan and decorin insofar as biglycan is a critical regulator of skeletal bone growth[6,16,93] and cardiac remodeling following myocardial infarction.[94] However, biglycan and decorin have functional commonality in the realm of regulating innate immunological responses.

BIGLYCAN LINKS THE SOLUBLE MATRIX WITH INNATE IMMUNE RESPONSES VIA TLR2/4 AND P2X SIGNALING

A groundbreaking discovery has been leading a revolution in further understanding biglycan biology.[6] Biglycan acts as an endogenous agonist for the innate immune receptors, Toll-like receptor 2 and 4 (TLR2/4) expressed on the surface of macrophages[95−97] (Figure 2), and can aggravate ischemic acute

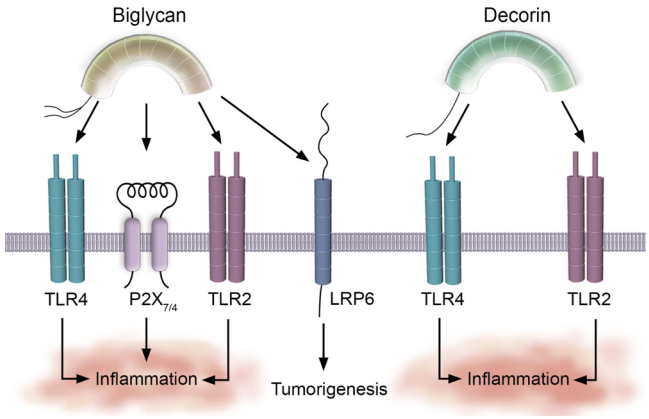

Figure 2. Biglycan and decorin bind innate immune system receptors for immunoregulation and tumorigenesis. The innate immune receptors TLR2 and TLR4 and the purinergic $P2X_{7/4}$ provide novel signaling circuits through which biglycan and decorin bind for regulating the innate immune system and cultivating a pro-inflammatory environment in sepsis and tumorigenesis. Biglycan also binds LRP6 for tumor promotion. Please see the text for more information.

renal injury.[28] As decorin is a soluble tumor repressor, biglycan has been identified as a soluble signaling molecule, a so-called "danger signal"[6,98,99] that interfaces with the innate immune system[33,74] following sepsis or ischemic injury. *De novo*-synthesized and secreted by circulating macrophages,[34,97] biglycan engages TLR2/4. This initiates a pro-inflammatory cascade that converges on NF-κB and evokes the synthesis and development of mature IL-1β,[96] and release of TNF-α and IL-6. Mechanistically, biglycan promotes receptor clustering and cooperativity of TLR2/4 with the purinergic $P2X_7$/$P2X_4$ receptors (Figure 2).[5,9,96] This affords rapid generation of reactive oxygen species that is directly involved in activating the NLRP3/ASC inflammasome.[96] Biglycan-mediated activation of the NLRP3/ASC inflammasome induces caspase-1-dependent cleavage of pro-IL-1β into mature IL-1β with subsequent secretion. Two feed-forward loops become established whereby biglycan promotes expression of *NLRP3* and *IL1B* transcripts,[96] and in turn, IL-1β and IL-6 can promote *BGN* expression and synthesis. Moreover, biglycan-mediated signaling via the MyD88/TRIF[34] arm downstream of TLR2/4 in kidneys results in CCL2 and CCL5 synthesis for the recruitment of macrophages and T-lymphocytes, respectively.[34,99,100] The CXCL class chemokines (e.g., CXCL1, CXCL2, and CXCL13) are subsequently released for macrophage[34,95] and B-lymphocyte conscription in murine lupus nephritis.[101] Biglycan, as a newly discovered DAMP, fundamentally connects soluble mediators derived from the matrix with regulating and inducing robust innate immune responses.

These observations have been elegantly confirmed *in vivo*.[6,8,9] Biglycan-deficient mice respond significantly less vigorously

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(e.g., decreased levels of active caspase-1 and lower titers of mature IL-1β) when challenged with inflammatory renal injury or lipopolysaccharide.[96] Physiologically, less IL-1β is found in the circulation, kidneys, and lungs.[96] Moreover, in a mouse model of ischemic acute kidney injury where biglycan was overexpressed, appreciably increased plasma and renal levels of TNF-α, CXCL1, CCL-2, and CCL-5 were found concomitant with an increased frequency of infiltrating macrophages, neutrophils, and T-lymphocytes.[97] Overall, this resulted in considerably worse renal function and paints biglycan as a key mediator of inflammatory renal disease.[28] Conversely, the impairment of renal function is markedly ameliorated in the compound knockout mouse lacking TLR2/4, indicating a crucial pathological role for the biglycan/TLR2/4 interaction *in vivo* (Figure 2).[97]

Biglycan also promotes a pro-inflammatory milieu within the lungs.[74] Under septic conditions, biglycan levels are substantially increased within cells infiltrating the pulmonary parenchyma.[95] In parallel with renal injury, biglycan deficiency dampens the immune cell population from breaching the lung tissue and results in less pulmonary damage.[95] Functionally, diminutive amounts of active caspase-1 and smaller amounts of mature IL-1β were found within the lungs.[96]

LOW-DENSITY LIPOPROTEIN RECEPTOR-RELATED PROTEIN 6 (LRP6) IS A TUMOR RECEPTOR FOR BIGLYCAN

Not unforeseeable, and consistent with the biological interactions (such as modulating Wnt signaling) mentioned above, biglycan is poised as a potent regulator of tumorigenesis and angiogenesis. Several solid malignancies are known to overexpress biglycan, which could contribute to tumor motility and even drug resistance.[102] The sources of biglycan in cancer currently remain elusive. However, it is known that TGF-β can induce biglycan from stromal fibroblasts.[102] Moreover, infiltrating immune cells (macrophages and neutrophils) constitutively secrete IL-1β and IL-6 under malignant conditions, and this will mechanistically support the feed-forward loop via TLR2/4 signaling.

Biglycan represents a functional dyad for the documented tumorigenic effects. Antiproliferative effects of biglycan stem from a study in which cells transformed with the Her2/Neu oncogene secrete decreased levels of biglycan in a PKC/CREB-dependent manner.[103] RNAi-mediated silencing of biglycan in the Her2/Neu transformed fibroblasts augments the growth rate and migration,[103] suggesting that biglycan can stymie the malignant phenotype conveyed by the Her2/Neu oncogene. However, biglycan can also compromise tissue architecture and integrity by promoting tumorigenesis via enhanced Wnt/β-catenin signaling.[91] Biglycan participates in a tripartite complex involving Wnt3a and the LRP6 (low-density lipoprotein receptor-related protein 6) coreceptor[91] (Figure 2). Biglycan enhances LRP6 phosphorylation as cells deficient in biglycan have a reduced level of cell surface retention of Wnt3a and a decreased level of LRP6 phosphorylation.[91] Collectively, this trimeric complex is sufficient for the canonical induction of β-catenin/TCF target genes and also transactivates the RUNX2 transcriptional complex in osteoprogenitor cells.[91] Finally, biglycan may also promote angiogenesis via enhanced VEGFA signal potentiation[92] and/or via the formation of reactive oxygen species downstream from TLR2/4-dependent signaling as a consequence of the NLRP3/ASC activation pathway (Figure 2).

DECORIN FOSTERS A PRO-INFLAMMATORY SIGNATURE VIA TLR2/4

Several lines of evidence have converged on the concept that decorin may also be involved in regulating immunological responses in a manner congruent with biglycan.[5,104] Decorin suppresses TGF-β, thereby repressing the macrophage phenotype via $p27^{Kip1}$ and $p21^{WAF1}$ induction,[105] promotes synthesis of the potent chemoattractant MCP-1,[106] and potentiates IFN-γ for allergen-induced inflammation.[107] In a mechanistic equivalence with biglycan function, LPS-induced sepsis greatly induces decorin expression in the plasma as well as in the perivascular regions and in bronchial epithelial cells,[32] whereas decorin deficiency attenuates the pro-inflammatory state induced by LPS.[32]

In a manner analogous to that of its relative, decorin binds TLR2/4 with high affinity on the surface of macrophages (Figure 2). Receptor binding initiates a pro-inflammatory cascade transduced by the MAPKs, ERK1/2 and the SAPK, p38 for the synthesis and secretion of TNF-α and IL-12p70.[32] Decorin also induces PDCD4 (programmed cell death 4), a translational repressor that post-transcriptionally suppresses the anti-inflammatory modulator, IL-10.[32] During active TGF-β signaling, microRNA-21 (miR-21) is in abundance and decreases levels of PDCD4, thereby permitting high levels of IL-10. Therefore, during LPS-induced sepsis, decorin levels increase and signal via TLR2/4 for TNF-α and IL-12p70 production, while concurrently blocking TGF-β from accessing the TGFβR. The sequestration of TGF-β by decorin circumvents miR-21-mediated repression of PDCD4, thereby allowing PDCD4 to translationally repress IL-10.[32] The total outcome of this intricate regulatory system advocates for the differential synthesis of pro-inflammatory immunomodulators while concurrently suppressing anti-inflammatory molecules and licenses decorin as a pro-inflammatory proteoglycan (Figure 2). This mechanism also operates within the tumor microenvironment and creates an inflammatory milieu that combats tumorigenic growth of established tumors via the differential regulation of PDCD4 and miR-21 and the secretion of TNF-α and IL-12p70.[32] Overexpressing decorin via adenovirus *in vivo* has provided robust evidence concerning the link among increased decorin abundance, the release of pro-inflammatory regulators, and the significant decrease in tumorigenicity.[32]

Collectively, these studies reveal entirely new roles for the circulating, soluble forms of biglycan and decorin in regulating and evoking protracted innate immune responses. Therefore, the importance of matrix-derived factors that would otherwise not be considered in the realm of immunology is furthered underscored by the range of homeostatic, physiologically relevant, and pathobiological processes these dynamic proteoglycans often contribute, coordinate, and stop.

BASEMENT MEMBRANE HEPARAN SULFATE PROTEOGLYCANS INTEGRATE SIGNALING OVER MULTIPLE RECEPTORS

The three best characterized basement membrane HSPGs (perlecan, agrin, and collagen XVIII) are functionally and structurally diverse participants that contribute nanostructural architecture for tissue stability, homeostasis, and tethering the pericellular matrix to the cell surface.[6,40] Primarily harboring heparan sulfate (HS) glycosaminoglycan chains, these HSPGs serve as sinks for multiple cytokines and growth factors.[6] Further, these elongated and multimodal molecules can act as

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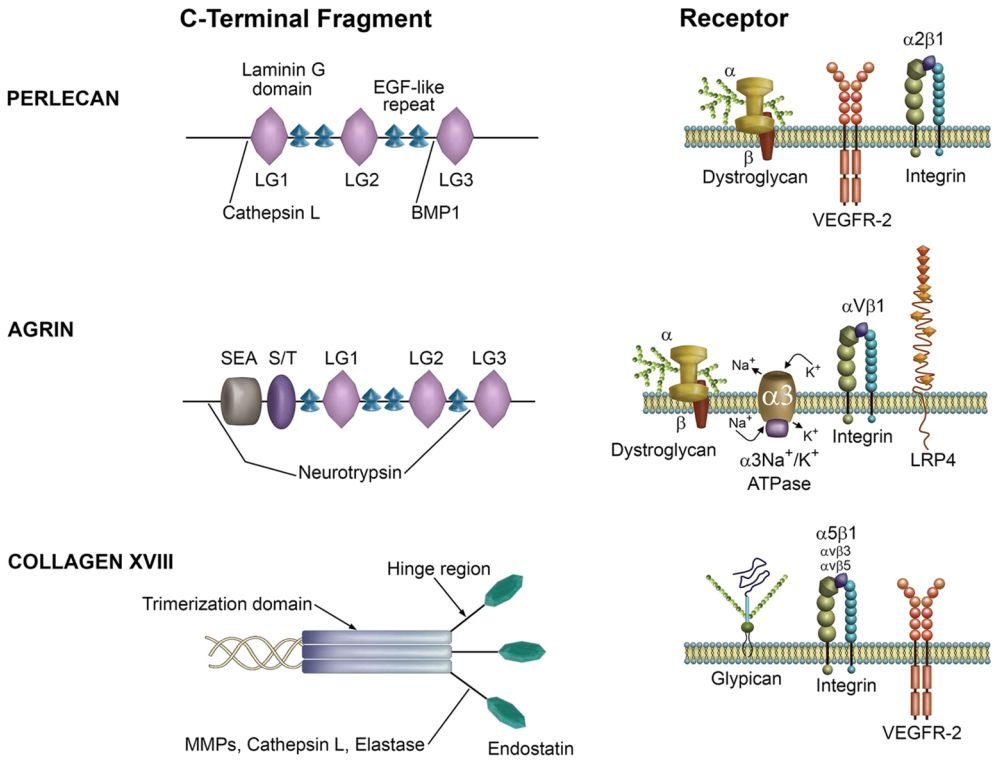

Figure 3. Basement membrane heparan sulfate proteoglycans ligate multiple receptors for effector function in a variety of cells and tissues. Graphical description of the C-terminal domains of the major basement membrane HSPGs demonstrating modular organization and architecture (left) and a summary of the primary receptors engaged (right). Figure adapted from ref 2.

coreceptors via HS-mediated presentation of growth factors in the proper orientation within three-dimensional space for optimal interactions with the cognate signaling receptor, e.g., FGF2/FGFR2.[108] Despite maintaining structural integrity as a network in basement membranes and presenting growth factors, perlecan, agrin, and collagen XVIII also signal in a manner independent of bound cytokines.[2,109] Indeed, each member can bind distinct and multiple cell surface receptors in a variety of tissues and microenvironments (Figure 3). Moreover, aberrant expression contributes significantly during pathobiological processes.

PERLECAN RECEPTORS: A DUAL-RECEPTOR ANTAGONISM

Perlecan is a gigantic (470 kDa protein core), multimodular HSPG, comprising five distinct protein modules, that exemplifies angiogenic bivalency by concealing pro- and anti-angiogenic properties within the same molecule.[2,110,111] Perlecan contributes positively by binding HS-interacting angiokines such as FGF2/7/18,[112] VEGFA, PDGF, and progranulin[113] and operates at multiple levels throughout developmental angiogenesis by modulating the VEGFA/VEGFR2 axis and $\alpha 2\beta 1$ integrin function.[114,115] Perlecan can also exert biomechanical antithrombotic properties.[116−119] Perlecan-null mice embryos are embryonic lethal and exhibit pericardial hemorrhage and deficits of the major cardiac vessels.[120,121] Seemingly, morpholino-mediated knockdown of perlecan in zebrafish shows a lack of angiogenesis and skeletal muscle defects.[122] In solid tumors, perlecan also contributes positively as a pro-angiogenic store of potent angiokines for rampant neovascularization via potentiated FGF2 and VEGFA signaling, resulting in unchecked tumorigenic growth and spreading.[2]

As a genuine diametric opposite, the most C-terminal domain of perlecan, known as endorepellin, confers potent inhibitory properties upon endothelial cells by specifically repelling (hence the eponym) migration and blunting capillary morphogenesis[123] (Figure 3). Exposure of recombinant endorepellin to stationary endothelial cells, both micro- and macrovascular, disrupts the actin cytoskeleton and decreases β-actin levels downstream of the $\alpha 2\beta 1$ integrin,[124,125] thereby providing a mechanism for its ability to block endothelial cell migration. Structurally, endorepellin recapitulates the modular architecture of the parent molecule by containing three laminin-like globular domains (LG1−LG3) each interspersed by tandem EGF-like motifs (Figure 3). Proteolytic cleavage of endorepellin from the parent perlecan molecule occurs following release of active cathepsin L from dying endothelial cells N-terminal to LG1.[19,126] However, in mast cells, evidence of a cotranscriptional mechanism involving alternative splicing of the primary perlecan mRNA transcript that ultimately yields functional endorepellin for regulating angiogenesis and wound healing exists.[127]

Upon liberation, soluble endorepellin engages in a novel form of suppression known as "dual-receptor antagonism" and functions as a molecular bridge by ligating the $\alpha 2\beta 1$ integrin and VEGFR2[128] for angiostasis. Simultaneous interaction of both receptors conveys high sensitivity and cell type specificity and wholly nullifies angiogenic responses *in vitro*[128] and *in vivo* by specific targeting of the tumor vasculature via the $\alpha 2\beta 1$ integrin.[129,130] Importantly, endothelial cells are the only cell type that express both receptors. Moreover, the BMP-1/Tolloid protease can release the bioactive fragment, LG3,[131] whose three-dimensional crystal structure has been determined.[132]

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The concept of "dual-receptor antagonism" is also exhibited by other proteolytically processed matrix components that yield soluble effectors [e.g., endostatin from collagen XVIII (see below)] for transducing and activating signaling programs fundamental for cellular behavior.

Physically, endorepellin interacts with VEGFR2 (between IgG domains 3 and 5 with an empirically derived K_d of 2.8 nM and in a region that overlaps with VEGFA binding) via the N-terminal LG1/2 domains while recruiting and binding the $\alpha2\beta1$ integrin with the C-terminal LG3 module via the $\alpha2$ I domain.[133] Mechanistically, this tethering brings the SHP-1 phosphatase, which is putatively bound to the cytoplasmic tail of the $\alpha2$ integrin subunit, into the functional proximity of the intracellular tails of VEGFR2 and executes rapid VEGFR2 dephosphorylation, inactivation, and ternary complex internalization[128,134,135] consisting of endorepellin, VEGFR2, and the $\alpha2\beta1$ integrin. Importantly, SHP-1 catalyzes dephosphorylation of Tyr1175 of VEGFR2,[136] a critical docking site for Shb and PLC-γ (see below).[135] Biologically, dual-receptor antagonism permits actin dissolution via the $\alpha2\beta1$ integrin, and angiogenic suppression via the downregulation of VEGFR2.[110] Downstream of simultaneous VEGFR2/$\alpha2\beta1$ binding and attenuation, multiple pro-angiogenic signaling pathways chiefly emanating from VEGFR2 are significantly compromised.[135] As discussed, endorepellin promotes active dephosphorylation, via SHP-1, of Tyr1175 of VEGFR2, thereby disrupting the recruitment, coupling, and activation of the angiogenic PI3K/Akt signaling axis. Impaired Akt (Ser473) signaling downstream of VEGFR2 manifests as blunted activation of PDK (Ser241), eNOS (Ser1177), and mTOR (Ser2448) despite the overabundance of exogenous VEGFA, suggesting that endorepellin competently and allosterically abrogates pro-VEGFA signaling.[135] The attenuation of mTOR signaling negatively impacted HIF-1α expression (a major downstream effector of mTOR) and activity in an oxygen-independent manner and, unbeknownst at the time, would be involved in a much more sublime manner (see below). Endorepellin also prevents PLC-γ/VEGFR2 docking (via diminished P-Tyr1175), resulting in the protracted attenuation of the PKC/JNK/AP1 signaling arm with concomitant attenuation of calcineurin activity and subsequent cytosolic retention of NFAT.[135] This dual-receptor antagonism suppresses key pathways for VEGFA expression and secretion.

Recently, a novel finding has expanded our understanding of the angiostatic function of endorepellin.[19] Endorepellin evokes endothelial cell autophagy in a VEGFR2- and Peg3-dependent manner under nutrient-enriched conditions[137] characterized by dually positive (e.g., Beclin 1/LC3) autophagosomes and the dynamic regulation of p62/SQSTM1. Perhaps the previous discovery of mTOR suppression (mTOR is staunchly anti-autophagic[138]) was prescient for endorepellin-evoked autophagy. Partial agonism is a recurring theme with soluble matrix constituents as endorepellin requires VEGFR2 signaling in much the same manner that decorin requires VEGFR2 kinase activity for Peg3-dependent autophagy.[137] Intriguingly, truncated endorepellin consisting of only LG1/2 was sufficient for Peg3, Beclin 1, and LC3 induction and autophagosome formation that subsequently incorporates these pro-autophagic mediators.[19,137] Endorepellin solely requires an interaction with VEGFR2 for endothelial cell autophagy; the LG3/$\alpha2\beta1$ interaction appears to be dispensable and perhaps even inhibitive[137] (Figure 3). Functionally, distinct signaling pathways are either activated or attenuated following dual-receptor antagonism and thereby holds physiological relevance. A molecular dissection of endorepellin revealed a profound dependence on LG1/2 for autophagic induction and angiogenic suppression; however, inhibiting cell motility relies heavily on the $\alpha2\beta1$-mediated arm. Therefore, we postulate that endorepellin-mediated prolonged autophagic induction may underlie its ability to suppress angiogenesis.

Clinically, endorepellin is released under physiological conditions,[139] whereas LG3 is a candidate serological biomarker that has been amply identified under many pathological conditions, including breast cancer and allograft rejection.[140−145] Moreover, LG3 possesses intrinsic angiostatic abilities via calcium regulation[131] through the $\alpha2\beta1$ integrin. Additional binding partners of endorepellin include the α/β-dystroglycan complex whereby perlecan[146] and agrin[147] (see below) are interacting partners[148] (Figure 3). Specifically, the proximal LG1/2 modules of endorepellin contain high-affinity binding sites for α/β-dystroglycan binding in maintaining skeletal muscle integrity[2] and may have a role in the development of ameloblastoma.[149] Disrupting perlecan:α/β-dystroglycan interactions compromises basement membrane stability.[150] Recently, it was discovered that perlecan is recruited to the nodes of Ranvier and participates in rapid neural conduction.[151] Dystroglycan selectively recruits perlecan as a novel component of the nodal matrix and is involved in nodogenesis via gliomedin clustering[151] (Figure 3). Overall, these findings propose a novel role for protein core fragments of basement membrane HSPGs in concurrently affecting cell adhesion and pro-angiogenic signaling receptors. The convergence of signaling toward a pro-autophagic pathway could exacerbate the growth of vascular cells and thus contributes to the angiostatic properties of endorepellin and perhaps other bioactive protein modules such as endostatin (see below).

AGRIN: A SYNAPTIC PROTEOGLYCAN THAT ENGAGES A DIVERSE ARRAY OF RECEPTORS

Structurally, agrin appears to be similar to the aforementioned proteoglycan, perlecan. Agrin is a multimodular HSPG with up to three HS that are apparently dispensable for function.[152] The agrin protein core has an additional complexity conveyed by alternative splicing of the *AGRN* mRNA.[153] Substitution of the N-terminal domain of agrin via an alternatively spliced mRNA converts agrin into a type II transmembrane proteoglycan[154] and can modulate Fyn and MAPK signaling pathways.[155] Chiefly involved in forming and maintaining homeostasis of neural and neuromuscular synapses,[156] agrin can also modulate neurite and motor neuron outgrowth via FGF2 binding,[157,158] and retinal development.[159] In combination with perlecan, agrin promotes oral squamous cell carcinoma[160] and also accumulates in HCC[161] with dynamic expression in cholangiocarcinoma.[162]

Agrin can be proteolytically cleaved by MMPs[163] and by the serine protease neurotrypsin immediately upstream of the SEA domain and distally between LG2 and LG3[164,165] (Figure 3). Processing generates 110, 90, and 22 kDa fragments of agrin.[2] Intriguingly, the processed fragments flanked by the neurotrypsin sites bear a striking resemblance to the C-terminal perlecan fragment, endorepellin [Figure 3 (see a section above)], which harbors the majority of the interaction sites [similar to perlecan and collagen XVIII (see below)]. Intact or proteolytically processed agrin interacts with several receptors with the caveat that specific splice variants of agrin bind specific cell surface receptors.[2,166,167] Agrin is an avid binding partner of

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the critical cell adhesion glycoprotein α/β-dystroglycan in muscle and non-muscle tissues alike.[147] Mutations that disrupt or result in inappropriate glycosylation of the membrane-localized α/β-dystroglycan complex have been implicated in a broad spectrum (ranging from mild to severe) of muscular dystrophies. The formation of the α/β-dystroglycan heterodimer represents the fundamental component responsible for linking extracellular matrix constituents (e.g., perlecan, agrin, and laminin) with dystrophin. These interactions primarily occur via carbohydrate moieties appended to the α/β-dystroglycan core complex by LARGE, which is necessary for proper α/β-dystroglycan function.[168] This interaction is obligatory for agrin-mediated clustering of acetylcholinesterase at neuromuscular junctions[169] in conjunction with perlecan. Recently, agrin-binding dystroglycan has been implicated in promoting synaptic plasticity and specialized GABAergic synapses.[170] Further, α/β-dystroglycan exhibits a high affinity with a large stretch of the C-terminal portion of agrin that has been alternatively spliced in a manner that excludes the Y and Z inserts.[171] These inserts, if present, negatively regulate association of agrin with α/β-dystroglycan.[171] Agrin also interacts with the α/β-dystroglycan receptor in the formation of immunological synapses with lymphocytes and aids in activation[172] as well as maintaining monocyte cell survival downstream in an α-dystroglycan-dependent manner.[173]

A second receptor for agrin has been identified as the $\alpha 3Na^+/K^+$-ATPase, which functions primarily as a neuronal ion pump for maintaining proper membrane potential[174] (Figure 3). Agrin-binding $\alpha 3Na^+/K^+$-ATPase (interestingly, resting neuronal synapses harbor a small percentage of agrin/$\alpha 3Na^+/K^+$-ATPase complexes) on pre- and postsynaptic neurons inhibits ion pump activity and results in a net loss of membrane polarization and a corresponding increase in neuronal action potential.[174] Because cardiac tissue expresses both agrin and the $\alpha 3Na^+/K^+$-ATPase, it is more probable that agrin has a role in cardiac pathology (e.g., congestive heart failure) via the pro-inotropic effects of agrin-mediated $\alpha 3Na^+/K^+$-ATPase modulation.[174] A third receptor, the $\alpha V\beta 1$ integrin, binds the LG2 domain of agrin and aids in proper synaptic localization of agrin (Figure 3).[175] The $\alpha V\beta 1$ integrin was discovered in a screen for interacting agrin partners, which revealed that $\alpha V\beta 1$ binds the second of three LG (LG2) domains. Further, agrin also contains a distinct $\beta 1$ interaction motif in the last EGF (EGF4) repeat.[175] The interaction of agrin with neurons is seemingly dependent on integrin and divalent cation (Mg^{2+}) as EDTA and monoclonal blocking antibodies directed against these sites substantially abrogated neuronal adhesion to agrin.[175] Moreover, $\alpha V\beta 1$ modulates the ability of agrin to appropriately cluster AChR on the surface of myotubes at neuromuscular junctions, orchestrates cation coordination for proper cell–matrix adhesion, and may also fine-tune agrin-directed neurite outgrowth.[176]

A fourth receptor, LRP4 (low-density lipoprotein receptor-related protein 4), is the agrin receptor responsible for MuSK (muscle-specific receptor tyrosine kinase) phosphorylation that permits appropriate AChR clustering at the neuromuscular junction[177] (Figure 3). Unlike binding α/β-dystroglycan, the Z-insert and the C-most terminal LG domain (LG3) are sufficient for LRP4 binding and downstream activation of MuSK.[177] Using SILAC quantitative proteomics, a role of the agrin/LRP4/MuSK signaling axis has been determined as a driving oncogenic force in the development of hepatocellular carcinoma.[178]

Unfortunately, the downstream signaling effectors for the agrin receptors remain elusive and very poorly understood for this versatile proteoglycan. Deciphering the downstream apparatuses will open novel therapeutic avenues for mitigating agrin pathologies (e.g., muscular dystrophies). However, despite this lack of basic signal transduction knowledge, the agrin LG3 domain has been used as a biomarker, akin with the LG3 domain of perlecan as a serological marker, as a method of detection of prematurely ruptured fetal membranes.[179]

COLLAGEN XVIII: A UNIQUE HSPG THAT HARBORS ENDOSTATIN

Collagen XVIII is a unique HSPG[180] that contains 10 interrupted collagenous domains flanked by noncollagenous regions localized at the N- and C-termini.[2] Collagen XVIII, a member of the multiplexin gene family,[181] is a homotrimer comprising three identical $\alpha 1$ chains, encoded by the *COL18A1* gene. It also harbors consensus sites for the attachment of HS chains.[182] Despite the multifactorial nature of this particular proteoglycan and the nearly global expression pattern of *Col18a1* within vascular basement membranes, mice lacking collagen XVIII are not embryonic lethal and are fertile,[183] suggesting it does not play a role in developmental vasculogenesis or angiogenesis. However, genetic ablation of *Col18a1* disrupts the structural integrity of the choroid plexus basement membrane and results in hydrocephaly.[184] A lack of *Col18a1* also causes hypertriglyceridemia in mice and humans[185] given modulation of LDL complexes within the subendothelial matrix via endostatin (see below).[186] Collagen XVIII is required for proper eye development,[2,183] vision, and retinal pigment function.[187] Moreover, collagen XVIII may have very specific and context-dependent roles for regulating angiogenesis[188] and tumor growth.[183] However, during HCC development, the level of collagen XVIII expression is decreased.[189]

Despite not having a large role in developmental angiogenesis and seemingly there being no enhanced tumorigenic growth upon genetic inactivation, collagen XVIII harbors a potent anti-angiogenic inhibitor, endostatin,[190−192] that completely neutralizes tumorigenic growth in various models.[191,193] As mentioned above, collagen XVIII is composed of three identical $\alpha 1$ chains. Each chain has an NC1 (noncollagenous 1) region that includes the trimerization domain, various sites sensitive to MMPs,[194] cathepsin L,[195] and elastase,[2,196] a hinge region, and the most C-terminal endostatin domain (Figure 3).[197−199] Endostatin orchestrates anti-angiogenic activities in a zinc-dependent manner.[200,201]

Mechanistically, endostatin binds multiple endothelial cell-specific integrins (e.g., $\alpha 5\beta 1$, $\alpha V\beta 3$, and $\alpha V\beta 5$)[202,203] and exhibits low-affinity interactions with glypicans.[204] In analogy to the bioactivity of endorepellin, endostatin also binds VEGFR2[205] (Figure 3) and can suppress *VEGFA* and *Myc* expression.[199,206] Ligation of endostatin with the cognate receptor results in a total hijacking of the malignant gene expression programs and counteracts tumorigenicity by reprogramming the responsive cells that ultimately interfere with endothelial cell migration and survival. As an additional mechanism of endothelial cell regulation, endostatin is one of a newly emergent class of proteoglycans that regulates autophagy[19,207] in an $\alpha 5\beta 1$-dependent manner,[207] resulting in apoptosis.[208] Indeed, loss of Beclin 1 exacerbates hypoxia-driven angiogenesis,[209] while the induction of autophagy, in turn, inhibits tumorigenesis in a Beclin 1-dependent manner.[210] Therefore, endostatin-mediated autophagy, via Beclin 1

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function, may ameliorate hypoxia-driven angiogenesis in an autophagy-dependent manner.

Collectively, these studies stress an important concept; that is, fragments of basement membrane HSPGs, which are located close to the plasma membrane, are in constant dialogue with signaling receptors, and their liberation from a matrix-bound state during tissue remodeling would have a strong effect on cell behavior.

CONCLUSIONS

Our aggregate knowledge concerning the underlying fundamental molecular and cellular mechanisms governed by interactions between soluble matrix constituents and cell surface receptors is growing at an exponential rate. Since the initial pioneering discovery that a considerable fraction of decorin is soluble and engages EGFR via high-affinity interactions and compromises oncogenic intracellular signaling, numerous similar paradigms have emerged as functional explanations for a variety of biological phenotypes.[6] The most recent example is lumican, a class II SLRP implicated in cancer and angiogenesis,[211] which promotes wound healing via direct ALK5 (TGFβ receptor 1) binding and activation.[212] Integrating signaling among multiple receptors, where each receptor is differentially expressed, cognizant of the cell- and tissue-specific resident microenvironment, and the empirically computed differential binding constants, licenses decorin (and related SLRPs) with an ability to affect a wide variety of processes. The perceived promiscuity of decorin is an inherent and critical facet of decorin (and related SLRPs) biology. We should point out that Myc is capable of regulating 1500 genes, and this ability is widely accepted in the literature. We propose that some matrix proteoglycans, because of their structure endowed with leucine-rich repeats, are designed to interact with other proteins and several RTKs, many of which contain Ig-like repeats (VEGFR2, etc.) or leucine-rich repeats (TLR2/4). Canonically, decorin has been viewed as an obligate antagonistic ligand for the EGFR and Met for tumorigenic and angiogenic suppression.[16,50] With the new dawn that decorin evokes endothelial cell autophagy and tumor cell mitophagy by interacting with VEGFR2 and Met, respectively, the effector landscape has shifted and decorin seemingly acts as a partial agonist for autophagic-mediated tumorigenic and angiogenic abrogation.[14,18,80] Mounting evidence suggests the requirement of the tyrosine kinase domain for proficient signal transduction and autophagic and mitophagic induction and ensuing angiostasis. Moreover, the case of IGF-IR epitomizes the concept of context- and environment-dependent signaling in normal, genomically stable cells when compared to transformed cells.

Decorin has long been heralded as a pan-RTK inhibitor that potently opposes tumorigenesis and angiogenesis in a multitude of solid tumors. However, in analogy with biglycan, decorin engages the innate immune receptors TLR2/4 and evokes a pro-inflammatory phenotype. Biglycan and decorin have been implicated in regulating immune responses during ischemic acute renal diseases, fibrosis, and tumorigenesis.[9] Indeed, generating a pro-inflammatory milieu within the tumor stroma appears as an additional layer of activity for the tumoricidal functions of decorin. Interestingly, transcriptome-wide analysis of basal breast carcinoma tumor xenografts following systemic administration of decorin protein core has shown a suppression of multiple immunoregulatory genes within the tumor stroma.[51] Conversely, soluble biglycan signaling via LRP6 potentiates canonical Wnt signaling and may contribute to enhanced cancer growth and progression via β-catenin-driven tumorigenesis.

Lastly, the pericellular matrix, responsible for organizing and maintaining the basement membrane structure and reliability in a multitude of tissues, directly participates in regulating centrally conserved cellular processes such as synaptogenesis, nodogenesis, autophagy,[80] angiogenesis, and tumorigenesis. Perlecan, agrin, and collagen XVIII are unique insofar as being multifunctional effectors that are proteolytically processed and yield modular effector units.[2] These soluble fragments can bind multiple receptors as diverse as integrins, glypicans, and RTKs for exercising their inherent biological functions across an array of tissues and maladies. Commanding a comprehensive understanding of the intricacies of proteoglycan signaling via this specialized, but ever-expanding, community of proteoglycan receptors will permit more personalized and targeted therapeutic options that will effectively combat our most insidious and devastating diseases.

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Notes

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ABBREVIATIONS

SLRP, small leucine-rich proteoglycan; RTK, receptor tyrosine kinase; HUVEC, human umbilical vein endothelial cells; ECM, extracellular matrix; HS, heparan sulfate; HSPG, HS proteoglycan; EGF, epidermal growth factor; EGFR, EGF receptor; IGF-I, insulin like growth factor I; IGF-IR, IGF-I receptor; VEGFA, vascular endothelial cell growth factor A; VEGFR2, VEGF receptor 2; PDGFR, platelet-derived growth factor receptor; TLR, Toll-like receptor; LPS, lipopolysaccharide; PDCD4, programmed cell death 4; MAPK, mitogen-activated protein kinase; LRP6, low-density lipoprotein receptor-related protein 6; ERK1/2, extracellular regulated kinase 1/2; SAPK, stress-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositidyl-3-kinase; HIF-1α, hypoxia inducible factor-1α; NFAT, nuclear factor of activated T-cell; NFκB, nuclear factor κB; MMP, matrix metalloproteinase; TSP-1, thrombospondin-1; TIMP-3, tissue inhibitor of metalloproteinase-3; AMPKα, AMP-activated protein kinase α subunit; DAMP, damage-associated molecular patterns; MCP-1, monocyte chemoattractant protein-1; SHP-1, Src homology region 2 domain-containing phosphatase-1; LRP4, low-density lipoprotein receptor-related protein 4;

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MuSK, muscle-specific receptor tyrosine kinase; AChR, acetylcholinesterase receptor; HCC, hepatocellular carcinoma; LRP-1, lipoprotein receptor-related protein 1.

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