Proteoglycan form and function: A comprehensive nomenclature of proteoglycans

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Abstract

We provide a comprehensive classification of the proteoglycan gene families and respective protein cores. This updated nomenclature is based on three criteria: Cellular and subcellular location, overall gene/protein homology, and the utilization of specific protein modules within their respective protein cores. These three signatures were utilized to design four major classes of proteoglycans with distinct forms and functions: the intracellular, cell-surface, pericellular and extracellular proteoglycans. The proposed nomenclature encompasses forty-three distinct proteoglycan-encoding genes and many alternatively-spliced variants. The biological functions of these four proteoglycan families are critically assessed in development, cancer and angiogenesis, and in various acquired and genetic diseases where their expression is aberrant.

Keywords

Proteoglycan; Glycosaminoglycan; Cancer growth; Angiogenesis; Growth factor modulation

Introduction

It has been nearly 20 years since the original publication of a comprehensive classification of proteoglycan gene families [1]. For the most part, these classes have been widely accepted. However, a broad and current taxonomy of the various proteoglycan gene families and their products is not available. In contrast to the classification of glycosaminoglycans (GAGs), primarily based on the chemical structure of their repeating disaccharide units, classifying proteoglycans is a much more complex task [2]. We propose a comprehensive and simplified nomenclature of proteoglycans based on three criteria including: Cellular and subcellular location, overall gene/protein homology, and the presence of specific protein modules within their respective protein cores. Whereas the first two attributes have been utilized in the past for various nomenclatures, the third attribute is of more recent
development and represents a sort of “intrinsic signature” for various protein cores. Indeed, modular design is based on the simple concept that protein cores are made up of finite units, like pieces of Lego. The units represent a minimum level of organization and a module can be thought of as a functional domain that affects cell–matrix dynamics. Another key feature is that each module/functional unit can be stable and can fold on its own, without being part of the large precursor protein. Thus, a module is a self-contained component. An example of this is the LG3 domain of endorepellin, the C-terminal globular-like domain of perlecan, which has recently been crystallized [3]. Below, we will critically assess the field of proteoglycans which now encompass forty three distinct genes and a much higher number of proteoglycans due to alternative splicing, thereby providing a very rich and biologically-active group of molecules. As hyaluronan and the enzymes involved in the synthesis and degradation of various GAGs are not covered in this review, readers are referred to recent reviews covering these closely-related subjects [4–18].

General features

Four major proteoglycan classes encompass nearly all the known proteoglycans of the mammalian genome (Fig. 1). Observing the types of proteoglycans based on cellular and subcellular localization, we can see that there is only one intracellular proteoglycan, serglycin. This unique proteoglycan forms a class on its own as it is the only proteoglycan that carries heparin side chains. Serglycin is packaged in the granules of mast cells and serves as biological glue for most of the intracellular proteases stored within the granules [19]. Another general observation is that heparan sulfate proteoglycans (HSPGs) are prevalently associated with the cell surface or the pericellular matrix. The HSPGs are intimately associated with the plasma membranes of cells, either directly via an intercalated protein core or via a glycosyl-phosphatidyl-inositol (GPI) anchor, and function as major biological modifiers of growth factors such as FGF, VEGF and PDGF among others. Similar functions are also performed by the HSPGs located in the basement membrane zone, in addition to their ability to interact with each other and with key constituents of the basement membrane, including various laminins, collagen type IV, and nidogen. Presentation of growth factors to their cognate receptors in a biologically-favorable form is a major function of cell surface and pericellular HSPGs. Another key role is participating in the generation and long range maintenance of gradients for morphogens during embryogenesis and regenerative processes.

As we move away from the cells in a centrifugal manner, chondroitin- and dermatan sulfate-containing proteoglycans (CSPGs and DSPGs, respectively) predominate. These proteoglycans function as structural constituents of complex matrices such as cartilage, brain, intervertebral discs, tendons and corneas. Thus, among other functions, they provide viscoelastic properties, retain water and keep osmotic pressure, dictate proper collagen organization and are the main molecules responsible for corneal transparency. The extracellular matrix also contains the largest class of proteoglycans, the so-called small leucine-rich proteoglycans (SLRPs) which are the most abundant products in terms of gene number. These SLRPs can function both as structural constituent and as signaling molecules, especially when tissues are remodeled during cancer, diabetes, inflammation and atherosclerosis. SLRPs interact with several receptor tyrosine kinases (RTKs) and Toll-like
receptors, thereby regulating fundamental processes including migration, proliferation, innate immunity, apoptosis, autophagy and angiogenesis. Below we will discuss the rationale for grouping certain proteoglycans in the same class and their overall biological function.

**Intracellular proteoglycans**

It is quite amazing that since the original cloning of serglycin, the first proteoglycan-encoding gene to be sequenced, no other true intracellular proteoglycan has been discovered. Serglycin occupies a class of its own insofar as it is the only proteoglycan that is covalently substituted with heparin due to its consecutive (and quite unique) Ser-Gly repeats, essentially a silk-like sequence. Serglycin has been utilized primarily by mast cells for the proper assembly and packaging of the numerous proteases that are released upon inflammation [19]. The defects in the formation of mast cell granules observed in Serglycin-deficient mice are remarkably similar to those observed in mast cells derived from mice lacking N-deacetylase/N-sulfotransferase 2, a key enzyme involved in the sulfation of heparin [19]. Thus, serglycin promotes granular storage via electrostatic interaction between its highly-anionic heparin chains and basic residues within the various proteases of the secretory granules. It is becoming evident, however, that all inflammatory cells express serglycin and store it within intracytoplasmic granules where, in addition to proteases, serglycin binds and modulates the bioactivity of several inflammatory mediators, chemokines, cytokines and growth factors [20].

More recently, serglycin has been found in a wide variety of non-immune cells such as endothelial cells, chondrocytes and smooth muscle cells [21]. Cell-surface serglycin promotes adhesion of myeloma cells to collagen I and affects the expression of MMPs [22]. These findings have been corroborated by *in vivo* studies where serglycin knockdown attenuates the multiple myeloma growth in immunocompromised mice [23]. It has been proposed that some of these effects are mediated by a specific interaction between serglycin and cell-surface CD44 [23], a known receptor for hyaluronan [24,25]. It has been recently shown that serglycin is a key component of the cell inflammatory response in activated primary human endothelial cells as both LPS and IL-1β increase its synthesis and secretion [26]. Notably, serglycin can be substituted with chondroitin sulfate (CS), and in several circulating cells serglycin contains lower sulfated CS-4 chains [21]. In contrast, several hematopoietic cells (mucosal mast cells, macrophages etc.) express serglycin with highly sulfated CS-E. Although the significance of this phenomenon is not fully appreciated, it is likely that these isoforms of serglycin might have different functions in a cell-context specific manner. Serglycin is a marker of immature myeloid cells and interacts with many bioactive components including histamine, TNF-α and proteases [27]. In general, serglycin expression correlates with a more aggressive malignant phenotype and it has been recently proposed that serglycin protects breast cancer cells from complement attack, thereby supporting cancer cell survival and progression [28].
Cell surface proteoglycans

In this class, there are thirteen genes, seven encoding transmembrane proteoglycans and six encoding GPI-anchored proteoglycans. With the exception of two gene products, NG2 and phosphacan, all contain heparan sulfate side chains.

Syndecans

The eponym syndecan was coined by the late Merton Bernfield [29] to define a class of transmembrane proteoglycans that would connect (from the Greek *syndein*, “bind together”) the surface of the cells to the underlying extracellular matrix. The syndecan family now comprises four distinct genes encoding single-pass transmembrane protein cores which include an ectodomain, a transmembrane region and an intracellular domain [4,30] (Fig. 2). The ectodomains exhibit the lowest amount of amino acid sequence conservation, no more than 10–20%, in contrast to the transmembrane and cytoplasmic domains which are 60–70% identical. A recent study has shown that the ectodomain of syndecans is natively disordered and this characteristic allows syndecans to interact with a variety of proteins and ligands, thereby providing enrichment in their biological function [31]. The ectodomain contains the GAG attachment sites, which are often covalently-linked to HS and sometimes to CS, making syndecans hybrid proteoglycans. Several cell types shed syndecan into the pericellular environment through the action of MMPs. For example, it has recently been shown that shed syndecan-2 retards angiogenesis by inhibiting endothelial cell migration [32], a key step in neovascularization [33]. The transmembrane domain contains a dimerization motif (GxxxG) that mediates both homo-dimerization and hetero-dimerization [30]. The intracellular domain is composed of two regions of conserved amino acid sequence (C1 and C2), separated by a central variable sequence of amino acids that is distinct for each family member (V) [34]. Notably, the C-terminus of all the four syndecans harbors a unique signature (EFYA) that binds PDZ-containing proteins. Generally, PDZ-containing proteins contribute to a proper anchor of transmembrane proteins to the cytoskeleton, thereby holding together large signaling complexes.

Syndecans are involved in a wide variety of biological functions, too vast to be reviewed here, but reviewed recently [5,30,34]. Briefly, syndecans bind numerous growth factors, especially through their HS chains, and dictate morphogen gradients during development. In concert with other cell-surface HSPGs, syndecans can act as endocytosis receptors and are also involved in the uptake of exosomes [35]. Syndecans play key roles as co-receptors for many RTKs and can also function as receptors for atherogenic lipoproteins [36]. Indeed, there is strong genetic evidence that syndecan-1 is the main HSPG mediating clearance of triglyceride-rich lipoproteins derived from either the liver or from intestinal absorption [37].

Many, if not all the syndecans, can also act as soluble HSPGs via partial proteolysis of their juxtamembrane region releasing their whole ectodomains. This shedding is considered a powerful post-translational modification that can regulate the amount of HSPG linked to the cell surface and that present in the pericellular microenvironment [30]. Several inflammatory cytokines can induce syndecan shedding by triggering outside-in signaling and by activating several metalloproteinases. In the case of hepatocytes, shedding of syndecan-1 occurs via PKC-dependent activation of ADAM17, and this impairs VLDL catabolism and promotes
hypertriglyceridemia [38]. Importantly, soluble syndecan-1 promotes the growth of myeloma tumors in vivo [39], and this process, i.e. the shedding of syndecan-1, is enhanced by heparanase [40], thereby offering a novel mechanism for promoting cancer growth and metastasis [41,42]. Notably, chemotherapy stimulates syndecan-1 shedding, a potential drawback of the treatment that could potentially favor tumor progression [43]. The biological interplay between heparanase-evoked shedding of syndecan-1 and myeloma cells leads to enhanced angiogenesis [44], further supporting cancer growth. As mentioned above, however, shed syndecan-2 inhibits angiogenesis via a paracrine interaction with the protein tyrosine phosphatase receptor CD148, which in turn deactivates β1-containing integrins [32], presumably α1β1 and α2β1, two main angiogenesis receptors. In contrast, the ortholog syndecan-2 is required for angiogenic sprouting during zebrafish development [45].

An emerging new role for syndecan-1 is linked to its ability to reach the nuclei in a variety of cells. Initial observations showed that myeloma and mesothelioma cells contain syndecan-1 in their nuclei [46,47] and this nuclear translocation is also regulated by heparanase [46], indicating that there must be a cellular receptor for shed syndecan-1 that could mediate its nuclear targeting and transport. In support of these studies are previous observations that exogenous HS can translocate to the nuclei and modulate the activity of DNA Topoisomerase I [48] and histone acetyl transferase (HAT) [49]. N-terminal acetylation of histones by HAT is linked to transcriptional activation, and this process is finely tuned by its counteracting enzyme, histone deacetylase (HDAC). Heparanase-evoked loss of nuclear syndecan-1 causes an increase in HAT enzymatic activity and enhances transcription of pro-tumorigenic genes [50]. Syndecan-1 that is shed from myeloma tumor cells is uptaken by bone marrow stromal cells and is transported to the nuclei by a mechanism that requires its HS chains, as this process is inhibited by heparin and chlorate [51]. Once nuclear, soluble syndecan-1 binds to HAT p300 and inhibits its activity, thereby providing a new mechanism for tumor–host cell interaction and cross-talk [52].

**CSPG4/NG2**

The melanoma-associated chondroitin sulfate proteoglycan (MCSP) was discovered over 30 years ago as a transmembrane proteoglycan and a highly immunogenic tumor antigen of melanoma tumor cells. This proteoglycan has been subsequently detected in various species, with many names designating the same gene product. The rat ortholog of MCSP is called nerve/glial antigen 2 (NG2) [53], while the term CSPG4 designates the human gene. We will use CSPG4/NG2 terminology with the idea that some of the functional properties have not been fully described in the human and rat species [54]. CSPG4/NG2 is a single-pass, type I transmembrane proteoglycan carrying one chondroitin sulfate chain, and harboring a large ectodomain composed of three subdomains (Fig. 2). The N-terminal domain (D1 subdomain) contains two laminin-like globular (LG) repeats. It is likely that the LG domains as in other proteoglycans (i.e. perlecan and agrin, see below) mediate ligand binding, cell–matrix and cell–cell interactions, as well as interaction with integrins and receptor tyrosine kinase (RTK). The central subdomain D2 contains 15 tandem repeats of a new module called CSPG [54]. The CSPG repeat is a cadherin-like and tumor-relevant module which is predicted to be involved in cell–matrix interaction, further modulated by the CS chain covalently attached to this module. Indeed, CSPG modules bind to collagens V and VI, FGF
and PDGF. The juxtamembrane subdomain D3 contains a carbohydrate modification able to bind integrins and galectin, as well as numerous protease cleavage sites. Accordingly, the intact ectodomain and fragments thereof can be detected in sera from normal and melanoma-carrying patients [54]. The transmembrane domain of CSPG4/NG2 is quite interesting insofar as it has a unique Cys residue, generally not found in transmembrane regions. The intracellular domain harbors a proximal region with numerous Thr phospho-acceptor sites for PKCα and ERK1/2, and a distal region encompassing a PDZ-binding module similar to the syndecan family. The latter can bind to the PDZ domain of several scaffold proteins involved in intracellular signaling, including syntenetin, MUPP1 and GRIP1.

Functionally, CSPG4/NG2 proteoglycan promotes tumor vascularization [55] and because of its predominant perivascular localization, CSPG4/NG2 may modulate the availability of FGF at the cell surface as well as the bioactivity and signal transduction of FGF receptors [56]. This CSPG binds to collagen VI in the tumor microenvironment and promotes cell survival and adhesion via the PI3K pathway [57]. Indeed, targeting CSPG4/NG2 in two animal models of highly-malignant brain tumors reduces tumor growth and angiogenesis [58]. Moreover, a combinatorial treatment using activated natural killer cells and a monoclonal antibody toward CSPG4/NG2 is capable of eradicating glioblastoma xenografts more efficiently than single therapies [59].

It has recently been discovered that NG2 controls the directional migration of oligodendrocyte precursor cells by constitutively stimulating RhoA GTPases [60]. Based on NG2 ability to regulate adhesion, RhoA GTPase and growth factor activities, it is likely that this transmembrane proteoglycan might play a key role in regulating cell polarity in response to extracellular cues [61].

**Perdido/Kon-tiki,** the *Drosophila* ortholog of mammalian *CSPG4*, genetically interacts with integrins during *Drosophila* embryogenesis, and its loss is embryonic lethal [62]. RNAi-mediated suppression of *Perdido/Kon-tiki* in the muscles, just before adult myogenesis starts, induces misorientation and detachment of *Drosophila* adult abdominal muscle, generating a phenotype similar to the embryonic lethal ones [63]. Thus, it is possible that, based on its high conservation through species, mammalian *CSPG4* could also play a role in myogenesis and function as well.

A recent study has added another function to CSPG4 by involving this cell surface proteoglycan in the pathogenesis of severe pseudomembranous colitis. CSPG4 acts as a receptor for the *Clostridium difficile* toxin B, one of the key toxins secreted by this gram-positive and spore-forming anaerobic bacillus [64]. The interaction occurs between the N-terminus of CSPG4 and the C-terminus of toxin B. This discovery, if confirmed in future studies, opens new therapeutic targets for the treatment of this severe and often lethal form of enterocolitis.

**Betaglycan/TGFβ type III receptor**

In 1991, two back-to-back papers reported on the isolation and cloning of a membrane-anchored proteoglycan with high affinity for TGFβ, and thus named betaglycan [65,66]. Betaglycan, also known as TGFβ type III receptor (TGFB3), is a single-pass transmembrane
proteoglycan that belongs to the TGFβ superfamily of co-receptors (Fig. 2). The extracellular domain contains several potential GAG attachment sites and protease-sensitive sequences near the plasma membrane. The short intracellular domain is highly enriched in Ser/Thr (>40%) and some of these residues are candidate sites for PKC-mediated phosphorylation [65]. Betaglycan amino acid sequence is highly similar to that of endoglin, a close member of the same superfamily.

The membrane-proximal ectodomain of betaglycan contains a unique module called zona pellucida (ZP)-C [67]. The ZP module is a structural element typically found in the ectodomain of eukaryotic proteins composed of a Cys-rich bipartite structure joined by a linker. Generally, proteins harboring ZP modules tend to polymerize and assemble into long fibrils of specialized extracellular matrices [67]. In the case of betaglycan and endoglin these ZP modules are not utilized for polymerization, rather they function as membrane co-receptors for the TGFβ superfamily members [68]. The intracellular domain contains a PDZ-binding element similar to that observed in the syndecan family of proteoglycans (Fig. 1).

Betaglycan is a ubiquitously-expressed cell surface proteoglycan that acts as a co-receptor for members of the TGFβ superfamily of Cys knot growth factors which also include activins, GDFs and BMPs [69,70]. For example, betaglycan enhances the binding of all the TGFβ isoforms to the signaling TGFβ complex [71] and is needed for TGFβ2 high-affinity interaction with the receptor complex. Betaglycan also blocks the aggressiveness of ovarian granulosa cell tumors by suppressing NF-κB-evoked MMP2 expression [72]. Betaglycan, together with other TGFβ-binding SLRPs, i.e. decorin and biglycan (see below), can be cleaved by granzyme B, thereby releasing an active form of TGFβ [73]. Ectodomain shedding of betaglycan is indeed necessary for betaglycan-mediated suppression of TGFβ signaling and breast cancer migration and invasion [74]. The ability of betaglycan to affect epithelial mesenchymal transformation [70], together with genetic evidence of embryonic lethality in Tgfbr3<sup>−/−</sup> mice, suggests that betaglycan may play a unique and non-redundant function during development.

Another important feature of betaglycan is its ability to modulate the subcellular topology of the signaling receptor complex via its PDZ-binding domain, which interacts with PDZ-containing proteins such as β-arrestin [75]. This interaction, as well as that between betaglycan intracellular domain and GIPC, would stabilize betaglycan at the cell surface and potentiate its bioactivity. Finally, betaglycan is involved in regulating many functions including reproduction and fetal growth [75], and is a putative tumor suppressor in many forms of cancer [76]. Several additional betaglycan-evoked activities have been recently reviewed elsewhere [75].

**Phosphacan/receptor-type protein tyrosine phosphatase β**

Phosphacan, originally isolated from rat brain, is a CSPG that interacts with neurons and neural cell-adhesion molecules (N-CAM) and corresponds to the soluble ectodomain of a Receptor-type protein tyrosine phosphatase β (RPTPβ) [77]. The phosphacan gene (PTPRZ1) encodes a single-pass type I membrane protein with a relatively large ectodomain harboring an N-terminal module homologous to the alpha-carbonic anhydrase (Fig. 2). Distal to this, there is a fibronectin type III domain. The ectodomain contains six Ser-Gly
repeats, at least four of which are flanked by acidic residues suggesting potential glycanation sites. Sporadically, phosphacan can also be substituted with keratan sulfate chains. Notably, alternative splice variants encoding different protein isoforms have been described but their full-length nature has not yet been established.

Functionally, the ectodomain of phosphacan mediates cell–cell adhesion by hemophilic binding. In addition, phosphacan’s ability to bind N-CAM and tenascin in a calcium-dependent manner suggests that RPTPs may also modulate cellular interactions via heterophilic mechanisms [77]. Indeed, phosphacan blocks the growth-promoting ability of N-CAM, axonin-1 TAG-1 and tenascin, and is crucial in the oriented movement of post-mitotic cells during cortical development of the brain [78]. Moreover, phosphacan binds contactin, another member of the Ig superfamily like N-CAM, and the extracellular portion of the voltage-gated sodium channel [79]. The latter interaction appears to be mediated by the carbonic anhydrase-like module of phosphacan’s ectodomain. It has been proposed that phosphacan, as an integral extracellular matrix constituent of the neural stem cell compartment, would contribute to the privileged microenvironment that supports self-renewal and maintenance of the neural stem cell niche [80].

Glypicans/GPI-anchored proteoglycans

Glypicans (GPC) are HSPGs that are bound to the plasma membrane via a C-terminal lipid moiety known as GPI, for glycosylphosphatidylinositol, linkage or anchor (Fig. 2). There are six independent genes in the mammalian genome which can be subdivided into two broad classes: GPC1/2/3/6 and GPC3/5 with orthologs present across Metazoan including Dally and Dlp in Drosophila melanogaster [81]. Although most of the protein core is unique to this family, there is a stretch of amino acid in the ectodomain of the protein core with similarity to the Cys-rich domain of Frizzled proteins. There are two unique features in the structural organization of all glypicans, with potentially important functional implications.

First and in contrast to syndecans, the attachment of the GAG chains – mostly HS chains – is located near the juxtamembrane region. This allows the three linear HS chains to span a great deal of plasma membrane surface, thereby presenting various morphogens and growth factors in an active configuration to their cognate receptors. Indeed, glypicans bind to and modulate the activity of Hedgehog (Hh), Wnt, and FGFs [82–84]. More recently, it has been shown that glypican-3 binds to Frizzled thereby acting directly in the modulation of canonical Wnt signaling [85].

Second, glypicans are dually processed via partial proteases and lipases. In the former case, the ectodomain of glypicans is processed via endoproteolytic cleavage by a furin-like convertase. This processing generates two subunits that are then bound via disulfide bonds, in a way similar to the Met receptor. In the latter case, the entire glypican proteoglycan is released from the plasma membrane via an extracellular lipase (Notum) that cleaves the GPI anchor. Drosophila studies have shown that the Notum-mediated release of glypican can regulate morphogen gradients including Wnt, BMP and Hh gradients [84].

Notably, the anchorless GPC-1, devoid of the GPI anchor, is a stable α-helical protein that rests high concentrations of urea and guanidine HCL [86]. Unfolding data are consistent
with a two-state model, suggesting that GPC-1 protein core is a densely-packed globular protein. In agreement with these data, the crystal structure of the *Drosophila* glypican *Dally-like* protein has revealed an extended α-helical fold [87]. The crystal structure of human GPC-1 is very similar to *Drosophila* Dally-like, and consists of a stable α-helical domain with 14 conserved Cys residues, followed by a GAG attachment site that is exclusively substituted with HS chains [88]. Of interest, removal of the α-helical domain leads to substitution with CS chains instead of HS chains, indicating that there is a “message” embedded in the α-helical domain that drives a different posttranslational modification [88].

Functionally, glypicans have been involved in the control of tumor growth and angiogenesis. For example, glypican-3 has been implicated in cancer and growth control. Human mutations of GPC3 cause the rare X-linked *Sympson–Golabi–Behmel* (SGB) syndrome, characterized by both pre- and post-natal overgrowth, abnormal craniofacial features, cardiovascular anomalies, renal dysplasia and urinary tract malformations [84]. Originally, it was hypothesized that GPC3 was an inhibitor of IGF-II, given the prominent function of IGF-II in developmental growth. However, it was later found that the levels of IGF-II do not change in *Gpc3*−/− mice nor does GPC3 interacts with IGF-II. It appears that GPC3 is an inhibitor of the Hh signaling, insofar as the Hh-dependent signaling activity is elevated in *Gpc3*−/− mice. Moreover, purified glypican-3 binds with high affinity to *Indian* and *Sonic Hh* as well as it competes with *Patched* for Hh binding [83,89]. A recent study has shown that processing by convertases is required for GPC3-evoked suppression of Hh signaling, and this process is dependent on the HS chains and their degree of sulfation [90]. Thus, the glypican family is not only complex in nature, but is also the control of various modifying enzymes (proteases and lipases) that modulate its biological activity. We are positive than many “surprises” will happen in the future regarding unsuspected biological functions of various glypicans.

**Pericellular and basement membrane zone proteoglycans**

This group of four proteoglycans is closely associated with the surface of many cell types anchored via integrins or other receptors, but they can also be a part of most basement membranes. Pericellular proteoglycans are mostly HSPGs and include perlecan and agrin, which share homology especially at their C-termini, and collagens XVIII and XV, which share homology at their N- and C-terminal noncollagenous domains (Fig. 1).

**Perlecan**

Perlecan is a modular HSPG encoded by a large gene [91,92] with a complex promoter [93–95]. The ~500-kDa protein core is composed of 5 domains with homology to SEA, N-CAM, IgG, LDL receptor and laminin [96,97] (Fig. 3). The terminal LG3 domain has been crystallized and reveals a jellyroll fold characteristic of other LG modules [3]. Perlecan is expressed by both vascular and avascular tissues [97–101], and is ubiquitously located at the apical cell surface [102,103] and basement membranes [98,104–106]. Perlecan regulates various biological processes primarily because of its widespread distribution [101,105] and its ability to interact with various ligands and RTKs [107], and more recently the potential utilization of perlecan splice variants in mast cells [108]. Perlecan is an early responsive...
gene and is induced by TGFβ [109] and repressed by interferon γ [95]. The heparan sulfate chains of perlecan and the protein core can be cleaved by heparanase and various proteases [110–112], respectively, releasing various pro-angiogenic factors [113].

Perlecan is involved in modulating cell adhesion [114,115], lipid metabolism [116], thrombosis and cell death [117,118], biomechanics of blood vessels and cartilage [119–121], skin and endochondral bone formation [122,123], and osteophyte formation [124]. Perlecan binds and modulates the activity of several growth factors and morphogens [106,125–129] and its expression is often deregulated in several types of cancer [130–134]. In Drosophila, perlecan, known as Trol (for terribly reduced optical lobe) regulates Fgf and Hh signaling to activate neural stem signaling [135,136]. In addition, Trol is essential for the architecture and maintenance of the lymph gland and for the proliferation of blood progenitor cells [137]. Loss of Trol is associated with premature differentiation of hemocytes and this phenotype can be rescued by ectopic expression of Hh [137]. In mice, Hspg2 controls neurogenesis in the developing telencephalon [138]. Moreover, perlecan can act as a lipoprotein receptor and mediate its endocytosis and catabolism [116]. Specifically, domain II of perlecan has been shown to bind low density lipoproteins and this interaction is mediated by the O-linked oligosaccharides [139], suggesting an important role for perlecan in atherogenesis and lipid retention.

Perlecan is a complex regulator of vascular biology and tumor angiogenesis [33,140,141] by performing a dual function: via the N-terminal HS chains, perlecan is pro-angiogenic [96] by binding and presenting VEGFA and various FGFs to their cognate receptors [33,141–152]. Moreover, heparanase-mediated cleavage of basement membrane perlecan releases FGF10 and enhances salivary gland branching morphogenesis [153]. Indeed, ablating Hspg2 or preventing Hspg2 expression in early embryogenesis causes severe cardiovascular defects [154–157]. The critical role for the N-terminal HS chains of perlecan has been elegantly demonstrated by the generation of mice harboring a genomic deletion of exon 3, designated Hspg2Δ3/Δ3 mice, which encodes the SGDs responsible for the covalent attachment of HS chains [158]. These mutant mice have impaired angiogenesis, delayed healing after experimental wounding and suppression of tumor growth [159]. When challenged with flow cessation of the carotid artery, the Hspg2Δ3/Δ3 mice show an enhanced intimal hyperplasia and smooth muscle cell proliferation [160,161]. Moreover, during mouse hind-limb ischemia, the HS chains of perlecan are key regulators of the angiogenic response [162]. Collectively, these studies reaffirm the role of HS perlecan in modulating pro-angiogenic factors such as FGF2, VEGFA and PDGF.

More recently other functions of perlecan have been discovered. Using a lethality-rescued Hspg2−/− where perlecan was reintroduced into the cartilage, it was found that perlecan deficiency leads to significant depression of endothelial nitric oxide synthase [163]. This leads to endothelial cell dysfunction, as shown by attenuated endothelial relaxation, likely as a consequence of endothelial nitric oxide synthase expression. This is another example of how a secreted HSPG affects the biology of vascular endothelial cells likely through a receptor-mediated signaling pathway. Another recently unveiled function of perlecan is its ability to bind the clustering molecule gliomedin [164]. In this case, perlecan binds dystroglycan at nodes of Ranvier which are required for fast conduction and accumulation of
Na+ channels. Perlecan seems to enhance clustering of nodes of Ranvier components via a specific interaction with gliomedin. Thus, perlecan may have specific roles in the biology and pathophysiology of peripheral nodes [164].

In contrast to the pro-angiogenic N-terminal domain I, the C-terminal processed form of perlecan domain V, named endorepellin [165], has a nearly opposite function: it inhibits endothelial cell migration, capillary morphogenesis, and in vivo angiogenesis [166–169]. A global proteomic analysis of human serum has identified endorepellin as a major circulating protein [170]. Moreover, endorepellin has been detected in extracts of fetal cartilage, exclusively in the hypertrophic zone, and it was speculated that processing of perlecan protein core in the growth plate could play a role in inhibiting blood vessel invasion or formation in cartilage [171]. Elevated endorepellin/LG3 peptides were found in the plasma proteome of patients with refractory cytopenia with multilineage dysplasia [172], and in the urine of end-stage renal failure patients [173]. These LG3 fragments had N-terminal residues (i.e., cleaved by BMP-1) identical to those reported by us [174]. Similar LG3 fragments are elevated in the urine of patients with chronic allograft nephropathy [175,176], in the amniotic fluid of pregnant women [177] with a marked increase in women with premature rupture of fetal membranes [178,179] and those carrying trisomy 21 fetuses [180]. Recently, LG3 peptides have been proposed to represent a potential marker of physical activity [181]. Endorepellin fragments have also been detected in the urine of children with sleep apnea [182], in the media conditioned by apoptotic endothelial cells [183,184], and in the secretome of pancreatic and colon carcinoma cells [185]. Endorepellin can be pro-angiogenic in brain infarcts due to the lack of anti-angiogenic α2β1 integrin and the presence of the pro-angiogenic α5β1 integrin receptor for endorepellin in brain microvascular endothelial cells [189]. In this context, LG3 can be released by oxygen-glucose deprivation and can be neuroprotective [190,191]. Finally, circulating LG3 levels are reduced in patients with breast cancer, suggesting that reduced LG3 titers might be a useful biomarker for cancer progression and invasion [192].

Mast cells produce shorter forms of perlecan including functional endorepellin, suggesting a potential role of endorepellin in inflammation and tissue repair [193]. Moreover, MMP-7 processing of perlecan in the prostate cancer stroma acts as a molecular switch to favor cancer invasion [112]. Thus, processed forms of perlecan protein core harboring domains III and IV can function as protumorigenic factors.

Endorepellin binds to the α2β1 integrin receptor [140,166,194], and tumor xenografts generated in α2β1−/− mice are insensitive to systemic delivery of endorepellin [168]. Endorepellin triggers the activation of the tyrosine phosphatase SHP-1 which, in turn, dephosphorylates and inactivates various RTKs including VEGFR2 [195]. Soluble endorepellin alters the proteomic profile of human endothelial cells [196], and exerts a dual receptor antagonism by concurrently targeting VEGFR2 and the α2β1 integrin [197]. Notably, the proximal LG1/2 domains bind the Ig3–5 domain of VEGFR2 while the terminal LG3 domain, release by BMP-1/Tolloid-like metalloproteinases [174], binds the α2β1 integrin [198]. This dual signaling causes: (a) Disassembly of actin filaments and focal adhesions, via the α2β1 integrin, leading to suppression of endothelial cell migration
More recently, we have discovered that endorepellin induces autophagy in endothelial cells via VEGFR2 signaling [201], similar to decorin (see below). This novel function could contribute to the angiostatic properties of this interesting fragment of perlecan protein core.

Agrin

The second pericellular/basement membrane HSPG is agrin. A C-terminal portion of agrin lacking HS chains was first isolated from the Torpedo electric organ as an agent responsible for acetylcholine receptor (AChR) clustering, thereby the eponym agrin, from the Greek ageirein, meaning “to assemble” [202]. The majority of the research on agrin in mammalians has focused on agrin’s contribution to the control of the postsynaptic apparatus in the neuromuscular junction. However, after many years of research, it was serendipitously discovered that agrin was indeed an HSPG interacting with N-CAM in the avian brain [203]. Subsequently, orthologs of agrin have been cloned from multiple species and are all highly homologous.

Agrin has a multimodular structural organization that is homologous to that of perlecan with potential generation of several splice isoforms. The N-terminal region can be spliced to generate either a Type II transmembrane form (TM) of agrin, highly expressed in nervous tissue, or an isoform associated with most basement membranes that contains the N-terminal-agrin (NtA) domain (Fig. 3). In the central nervous system, TM agrin is highly expressed by axons and dendrites; thus, neurite-associated TM agrin could potentially function as receptor or co-receptor for neurite function. The NtA domain has high affinity for the laminin γ1 chain’s coiled-coil domain, thereby functioning as a link between the cell surface and the basement membrane. Following the N-terminal domain is a stretch of nine follistatin-like (FS) repeats, also known as Kazal-type protein inhibitor domains [204]. The last two repeats are separated by an insertion of two laminin EGF-like (LE) domains. Notably, overexpression of TM agrin in non-neuronal cells induces filipodia-like processes similar to those induced in CNS neurites, and this bioactivity was localized to FS repeat seven [205]. Thus FS modules can modulate an important biological activity of neurons by affecting the reorganization of the actin cytoskeleton during active neurite growth.

Following the FS repeats, there are two Ser/Thr (S/T)-rich domains which can be alternatively spliced (especially the second ST module) to generate an X+/− form [204]. The two S/T modules are separated by a SEA module, similar to that of perlecan (see above), known to be involved in regulating O-glycosylation of mucins and glycoproteins. The N-terminal and central regions of agrin protein core contain the attachment sites for HS chains, and rotary shadowing electron microscopy has revealed three attachment sites for HS chains [206]. However, agrin can be a hybrid HS/CSPG with two clusters of Ser-Gly sequences, one primarily carrying HS chains located between FS repeats 7 and 8, and one carrying mostly CS chains, located in the first S/T module [207]. An agrin fragment harboring all protein modules described so far inhibits neuronal outgrowth independently of HS or CS [208]. The HS chains of agrin, however, bind FGF2, thrombospondin, β-amyloid peptide, N-CAM, and the protein tyrosine phosphatase δ [209].
The C-terminus of agrin is structurally organized as perlecan domain V/endorepellin, with three LG domains separated by EGF-like modules (Fig. 3). The only difference is the position of the EGF repeats vis-à-vis the LG domains. The LG domains of agrin bind α-dystroglycan in skeletal muscle and low-density lipoprotein-like receptor 4 (LRP4) [210]. The latter interaction activates the RTK MuSK which initiates a signaling cascade that leads to the formation of pre- and post-synaptic specializations. The terminal LG3 domain of agrin can be alternatively spliced with inserts of 8, 11 and 19 residues and their bioactivity is influenced by Ca\(^{2+}\) binding [211]. Moreover, the overall function of agrin is regulated by site-specific processing via MMPs [212]. Agrin is a good example, together with perlecan, of the evolved mechanisms in molecular recognition and function achieved through utilization of common protein folds, such as LG modules [211].

Thus, both agrin and perlecan bind, via their LG-rich C-termini, multiple cell surface receptors including RTKs, and can potently modulate cardiovascular and musculoskeletal systems. Importantly, conjugation of LG modules of agrin and perlecan to polymerizing laminin-2 evokes clustering of acetylcholine receptors [213]. These data provide strong support for a cooperative function of basement membrane HSPGs in AChR assembly and function.

Of interest, recessive missense mutations in the AGRN genes cause congenital myasthenic syndromes characterized by defective neuromuscular transmission [214]. More recently, AGRN recessive missense mutations have been identified as causative factor for a congenital myasthenic syndrome with distal muscle weakness and atrophy, resembling distal myopathy [215]. Given the large number and heterogeneous groups of neuromuscular disorders it is likely that in the future new syndromes will be identified that are linked to genetic abnormalities of the AGRN gene.

Collagens XVIII and XV

Collagens XVIII and XV, two members of the “multiplexin” gene family [216–220], harbor structural features of collagens and proteoglycans, being substituted with HS and CS, respectively [221]. Like agrin, collagen XVIII was serendipitously discovered to be an HSPG when monoclonal antibodies were used against an unidentified avian HSPG [222]. Subsequent cloning and sequencing of the cDNA showed that this avian HSPG protein core shows high homology to the mammalian collagen XVIII. Collagen XVIII is a homotrimer comprised of three identical α1 chains and consists of ten interrupted collagenous domains, flanked by eleven noncollagenous domains at their respective N- and C-termini. Collagen XVIII also harbors three Ser-Gly consensus binding sites for the attachment of HS chains [223] (Fig. 3). The human COL18A1 gene can generate three protein variants derived from alternative promoter usage and splicing events [221]. Specifically, COL18A1 can produce a short variant, a middle variant containing a TSP-1 module, and a long variant containing an additional Frizzled repeat. The latter is missing in collagen XV. Both collagens XVIII and XV contain a C-terminal noncollagenous domain harboring the antiangiogenic endostatin and endostatin-like modules. Specifically, the NC1 domain consists of an N-terminal trimerization region, a central hinge region sensitive to proteolytic activity and the C-terminal endostatin domain (Fig. 3). Endostatin interacts with numerous receptors including...
integrins α5β1, αvβ3 and αvβ5 [224,225] and VEGFR2 [226]. Interestingly, endostatin, in analogy to endorepellin, is capable of inducing autophagy in endothelial cells by modulating Beclin 1 and β-catenin levels [227]. These findings suggest that C-terminal anti-angiogenic fragments of pericellular HSPGs may evoke endothelial cell autophagy which could contribute to their angiostatic properties.

The signaling network evoked by soluble endostatin leads to a downregulation of several key components of the VEGF signaling cascade and, concurrently, to a stimulation of the synthesis of thrombospondin [228], a powerful angiostatic protein [229,230].

Both collagens XVIII and XV are ubiquitously expressed in all vascular and epithelial basement membranes of human and mouse tissues, with an overall topography reminiscent of that of perlecan and agrin. Notably, Col18a1−/− mice show multiple ocular abnormalities, especially affecting the anterior portion of the eyes [231,232]. In humans, mutations in the COL18A1 gene cause Knobloch syndrome, a rare autosomal recessive disease characterized by high myopia, vitreoretinal degeneration and retinal detachment [233,234].

Col18a1−/− mice show enhanced neovascularization and vascular permeability during atherosclerotic disease progression [235], and loss of this gene in both mice and humans leads to hypertriglyceridemia [236]. Moreover, Col18a1−/− mice display enhanced angiogenesis during wound healing [237]. In contrast to Col18a1−/−, Col15a1−/− show normal vascular formation but primarily develop a skeletal myopathy [238]. However, microscopic changes in the small arterioles with collapsed capillaries and endothelial cell degeneration in heart and skeletal muscles are also noted [238]. Collectively, these findings implicate collagen XVIII as a negative regulator of angiogenesis and as an anti-atherosclerotic factor. Collagen XV may function as a key structural constituent required for the stabilization of skeletal muscle cells and microvessels [238], and recently both collagens XV and XVIII have been involved in mediating the influx of leukocytes in renal ischemia/reperfusion [239]. Of interest, mice lacking the long form of collagen XVIII (i.e. the N-terminal frizzled-like sequence) but producing the short form, exhibit a decreased number of pre-adipocytes, hepatic steatosis and elevated VLDL and triglyceride levels [240]. Thus collagen XVIII is directly implicated in the generation of adipose tissue and in hyperlipidemia associated with visceral obesity and fatty liver.

Extracellular proteoglycans

This is the largest class encompassing 25 distinct genes. Four genes encode the hyalectans, key structural components of cartilage, blood vessels and central nervous systems. They all bind hyaluronan and form supramolecular complexes of high viscosity. The second class encompasses 18 SLRPs, which have a multitude of functions and often signal through various receptors as many members are now found in the circulation and in various body fluids. The third class, SPOCK family, encompasses 3 testicans which are calcium-binding HSPGs.
Hyaluronan- and lectin-binding proteoglycans (hyalectans)

Hyalectans comprise a distinct family of proteoglycans with structural similarities at both the genomic and protein levels. This family contains four distinct genes, namely aggrecan, versican, neurocan, and brevican (Figs. 1 and 4). A shared feature of these proteoglycans is their tridomain structure: an N-terminal domain that binds hyaluronan, a central domain harboring the GAG side chains, and a C-terminal region that binds lectins [2]. Based on this dual activity at the N- and C-termini, the term hyalectans, an acronym for hyaluronan- and lectin-binding proteoglycans, has been proposed [1]. Alternate exon usage and variability in the degree of glycanation and glycosylation provide diverse functional attributes for these proteoglycans which often act as molecular bridges between cell surfaces and extracellular matrices.

Aggrecan

Aggrecan, as its eponym indicates, has the propensity to aggregate into large supramolecular complexes > 200 MDa together with hyaluronan and link protein, and is the principal load-bearing proteoglycan of cartilage [241]. These large aggregates generate a densely-packed, hydrated gel enmeshed in a network of reinforcing collagen fibrils and other proteoglycans and glycoproteins [242]. The N-terminal domain contains four link protein-like modules or proteoglycan tandem repeats in addition to the Ig-like repeat (Fig. 4). The entire link module is ~100 amino acids in length and has a characteristic consensus sequence with four disulfide-bonded Cys residues. These modules form two globular domains known as G1 and G2 [243]. The G1 domain is related to link protein and to the other G1 domains of the hyalectans, both in terms of structural domains and subdomains [243]. The G1/hyaluronan/link protein ternary complex is very stable thereby immobilizing the aggrecan into enormous complexes that maintain a stable network and provide mechanical properties to cartilage. An interglobular region, between G1 and G2, has a rod-like structure and harbors several protease-sensitive sites involved in the partial degradation of aggrecan in arthritis and other inflammatory diseases.

Following the G2 domain is a relatively small region containing numerous KS chains. This domain is not well conserved and its size significantly varies among species. Next, is the largest domain of aggrecan which contains the GAG-binding region. This protein domain is encoded by a single, very large (~4 kb) exon with ~120 Ser-Gly dipeptide repeats, which can generate >100 covalently-linked CS chains. The concentration of negatively-charged forces within aggrecan accounts for its ability to hold large amount of water, not only in cartilage, but also in the intervertebral disc and brain. Moreover, electrostatic repulsion forces generated by the numerous negatively-charged CS and KS chains of aggrecan provide the equilibrium compressive modulus (a measure of stiffness) of cartilage. In humans, variable number of tandem repeats can generate different alleles in the general population, ranging between 13 and 33 repeats, causing a great variability in the aggrecan degree of glycanation and negative charge (due to sulfation) within cartilage.

The G3 module of aggrecan contains 2 EGF-like repeats, a C-type lectin domain and a complement regulatory protein (CRP) domain. Notably, the EGF repeats can be alternatively spliced in part because in rodents exon 13 is a pseudoexon. Moreover, in rodent brain, the
most common aggrecan species lacks both EGF repeats [244]. As in the case of other hyalectans, the C-type lectin domain of aggrecan binds simple sugars, such as fucose and galactose, in a Ca\(^{2+}\)-dependent manner. Thus, aggrecan G3 may serve as a binding domain for the galactose present on collagen type II or other extracellular matrix or cell surface constituents. Moreover, the G3 domain of aggrecan interacts with tenascins, fibulins and sulfated glycolipids [245]. Thus, aggrecan could bridge and interconnect various constituents of the cell surface and extracellular matrix via its C-terminal G3 domain, thereby providing a mechanosensitive feedback to the chondrocytes. Indeed, epiphyseal chondrocytes grown on hydrogel substrata can maintain their phenotype for up to six months with proper secretion of cartilage-specific constituents, such as aggrecan, and collagens type II and IX, but without expressing collagen type I [246].

The essential role of aggrecan in cartilage is underscored by several genetic defects including two autosomal recessive chondrodystrophies, nanomelia in chickens and cartilage matrix deficiency (cmd) in mice [247]. In nanomelia, the defect leads to the formation of a C-terminal truncated aggrecan, while in cmd mice there is an even larger C-terminal truncation. In both mutant animals, there is little or no aggrecan in cartilage leading to shortened long bones and lethality, most likely due to respiratory failure arising from tracheal collapse [247]. Aggrecan is also involved in the morphogenesis of limb synovial joints and articular cartilage [248], and fragments of aggrecan represent biomarkers for osteoarthritis [249].

Aggrecan is also expressed in the brain, and unlike other hyalectans, is expressed primarily in the perineuronal nets [79]. A relatively small number of cortical neurons express aggrecan, especially the cortical interneurons [244]. One of the hypothesized functions of brain aggrecan is its potential regulation of neural maturation, in addition to its physical ability to adduct cations and regulate osmotic imbalances. Thus, aggrecan could affect high-rate synaptic transmission, mechanical stabilization of synaptic contacts and neuroprotection by counteracting oxidative stress via scavenging redox-active cations [244].

**Versican**

Versican, an eponym that signifies its highly versatile function [250], is the largest member of the hyalectan family when expressed as a whole molecule, designated V0 (Fig. 4). Versican is the mammalian counterpart of the so-called PG-M, a large chondroitin sulfate proteoglycan expressed during chondrogenesis in chick limb buds [251,252]. The VCAN gene, originally called CSPG2 [253–255], encompasses 15 exons encoding a full-length (V0 variant) protein core of ~400 kDa, with 3396 amino acid residues. The overall structural organization of versican is similar to that of aggrecan, with a few exceptions. At the N-terminus there is only one globular domain instead of two. Specifically, the N-terminal domain of versican contains one IgG fold followed by two consecutive link protein modules similar to G1, which are involved in mediating the binding of proteins to hyaluronan. Recombinant versican and a truncated form of versican containing the N-terminal domain bind to hyaluronan with high affinity, \( K_D \sim 4 \text{ nM} \), in the same range as the other major aggregating CSPG, aggrecan [256]. The central domain of versican comprises two relatively large subdomains, designated GAG\(\alpha \) (encoded by exon 7) and GAG\(\beta \) (encoded by exon 8),
which can be alternatively spliced to generate the three main variants V1, V2 and V3 [255], with significant CS polymorphism in the different versican isoforms. These large regions lack Cys residues and contain ~30 potential consensus sequences for GAG attachment as well as several binding sites for N- and O-linked oligosaccharides. There is also variability in tissue expression of the isoforms, with V0 and V1 representing the most ubiquitous isoforms, expressed in the developing heart and limbs, vascular smooth muscle cells and several nonneuronal tissues, whereas the V2 isoform is mainly present in the brain [79]. Expression of the V3 isoform in arterial smooth muscle cells regulates multiple signaling pathways, including TGFβ, EGF and NF-κB pathways, thereby creating a microenvironment resistant to monocyte adhesion [257]. Recently, a new splice variant of Versican, V4, has been identified in human breast cancer, which contains up to five CS chains [258]. This isoform comprises only the first 1194 bp of exon 8 (encoding the GAGβ) sandwiched between exon 6 and 9, and is highly expressed in breast cancer in contrast to normal breast tissue where it is undetectable [258]. Notably, the avian versican ortholog harbors an additional exon, known as PLUS, in the N-terminal region that is developmentally regulated [259]. This exon can be alternatively spliced giving rise to two additional isoforms. Although no similar region is present in the mammalian genome, sequence homology suggests that the PLUS domain of avian versican may correspond to the KS attachment region in aggrecan.

The C-terminal domain of versican is also very similar to that of aggrecan and other hyalectans in that it harbors similar structural motifs, including two EGF-like repeats, a C-type lectin domain, and a complement regulatory protein-like module (Fig. 4). These motifs are generally found in the selectin family of glycoproteins, which include several adhesion receptors regulating leukocyte homing and extravasation during inflammation. Given the fact that the various C-type lectin modules may have different saccharide-binding specificities, the presence of these domains at the C-terminal ends of hyalectans could provide specialized and refined functions for these CSPGs. Moreover, these findings suggest that versican may form a molecular link between lectin-containing glycoproteins at the cell surface and extracellular hyaluronan. Because hyaluronan is bound to the cell surface via its CD44 receptor [241,260], versican may also stabilize a large supramolecular complex at the plasma membrane zone [2].

The functional roles of versican are multiple and complex. Versican is involved in the regulation of cell adhesion, migration and inflammation [260–262]. During an inflammatory response, leukocytes need to emigrate from the inner blood vessels into the damaged surrounding tissues. During this process, leukocytes encounter a provisional matrix highly enriched in versican, which in turn is capable of interacting with many receptors on the surface of immune cells including CD44, P-selectin glycoprotein-1, and Toll-like receptors [261]. Another important role of versican derives from the multiple processing of its protein core. Versican is degraded and partially processed by several MMPs, plasmin and members of the ADAMTS family [263,264]. Versican is also involved in the biology of leiomyosarcomas insofar as its levels are markedly increased vis-à-vis benign leiomyomas, and suppression of versican expression attenuates malignant growth and tumor progression [265].
Two autosomal dominant eye disorders, Wagner syndrome and erosive vitreo-retinopathy, which both show optically empty vitreous cavities, are caused by mutations in the \textit{VCAN}\textsuperscript{266}. Interestingly, the mutant alleles contain mutations around the splice sites flanking exon 8, which encodes the GAGβ domain, likely producing exon skipping. The ultimate consequence of exon skipping is that most tissues, and especially the eye, would have a lack of the GAGβ domain with much fewer CS chains, and thus a less charged environment.

**Neurocan and brevican**

The third member of the hyalectans is neurocan, a developmentally regulated CSPG originally cloned from rat brain, and thus its eponym to signify neuronal origin [267]. Rotary shadowing electron microscopy of neurocan has revealed two globular domains interconnected by a 60–90 nm rod [268], similar to the predicted organization of other hyalectans derived from biochemical and genomic analyses. As other hyalectans, neurocan has an N-terminal domain with structural homology to the typical arrangements found in link protein, harboring a G1 domain and an Ig repeat (Fig. 4). Functionally, recombinant N-terminal module of neurocan interacts with hyaluronan in solution, and isolated complexes comprise gel permeation assays, and hyaluronan and globular profiles [268]. Therefore, it is highly likely that all the N-terminal domains of the hyalectans bind and interact with hyaluronan and link protein in vivo, forming gigantic supramolecular aggregates. The next interglobular region of neurocan, with little homology to other proteins, contains ~seven potential CS binding sites. The C-terminal module of neurocan shares significant homology to the G3 domain of aggregcan and versican, with ~60% identity between the rat neurocan and human versican/aggrecan. By analogy to the other hyalectan members, this domain could bind several brain glycoproteins including Ng-CAM, N-CAM, and tenascin. Neurocan is known to inhibit neurite outgrowth in vitro and, in keeping with this function, the expression of neurocan is increased at the site of mechanical and ischemic injury in the adult central nervous system [78,269]. Neurocan has been implicated in path finding during development. However, \textit{Ncan}\textsuperscript{−/−} mice develop normally with only mild deficiency in long-term potentiation, suggesting that neurocan might only have a redundant role during development.

Brevican is one of the most important hyalectans of the central nervous system. It takes its eponym from the Latin word \textit{brevis} (for short) as it harbors a typical hyalectan configuration with N- and C-terminal homologous domains, but with the shorter GAG-binding domain (Fig. 4) [270,271]. Brevican was simultaneously discovered by three laboratories searching for hyaluronan-binding proteoglycans in the brain [271,272] and for synapse associated proteins [273]. The eponym BEHAB, which is sometimes used for brevican as they are the same gene products, refers to brain-enriched hyaluronan binding protein [272]. Although sequence homology with the other hyalectan members is quite uniform (~60% overall), the GAG-binding domain is poorly conserved and contains a high content of acidic amino acid residues (mainly glutamic acid). This structural feature, shared with the link protein-like module of versican, could mediate binding to cationic proteins and minerals. In analogy to neurocan, brevican can exist as either a full-length CSPG or as a partially cleaved product without the GAG-binding module and the N-terminal domain. Similar to neurocan, brevican...
exists in vivo either as a full-length proteoglycan or as a proteolytically-processed form lacking the GAG-binding region and the N-terminal domain. The C-terminal G3-like domain is structurally organized like the other hyalectans, although it harbors only one EGF-like repeat instead of two as in all the other members (Fig. 4).

In addition to secreted full-length brevican, an isoform of brevican encoded by a shorter 3.3 kb mRNA and highly expressed during post-natal development, is linked to the plasma membrane via a GPI anchor [273]. Notably, the GPI-anchored brevican lacks EGF, C-type lectin and CRP modules but contains a stretch of hydrophobic amino acids resembling the GPI-anchor. Brevican is located at the outer surface of neurons and is enriched at perisynaptic sites. Brevican interacts with tenascin-R and fibulin-2 via its G3-like domain [274].

Functionally, brevican has been implicated in glioma tumorigenesis, nervous tissue injury and repair, and in Alzheimer’s disease [274]. However, many more studies need to be performed before a clear picture of brevican’s biology can be clearly drawn.

**Small leucine-rich proteoglycans/SLRPs**

**General considerations**

This is the largest family of proteoglycans encompassing 18 distinct gene products and numerous splice variants and processed forms. The eponym SLRP, for small leucine-rich proteoglycans [1], is now a widely-used abbreviation. SLRPs designate a class of proteoglycans characterized by a relatively small protein core (as compared to the larger aggregating proteoglycans) of 36–42 kDa and encompassing a central region constituted by leucine-rich repeats (LRRs) (Fig. 5) [275]. The SLRPs are ubiquitously expressed in most extracellular matrices and are highly expressed during development in the thin membranes enveloping all the major organs such as meninges, pericardium, pleura, periosteum, perichondrium, perimesium and endomesium [276–278] This strategic topology suggests that SLRPs would be directly involved in regulating organ size and shape during embryonic development and homeostasis [279,280].

The 18 SLRP members are grouped into five classes: Classes I–III are canonical genes, whereas Classes IV and V are non-canonical (Fig. 1). Although eight non-canonical members do not carry glycosaminoglycan side chains, they have been included because they share close structural homology and several functional properties with the full-time proteoglycans. This classification is based on several considerations, including evolutionary conservation, homology at both the protein and genomic level, and chromosomal organization (Fig. 5A) [281]. It is important to note that SLRPs share many biological functions in terms of binding to various collagens [282–286], RTKs [287–290], innate immune receptors [291,292] and in terms of modulating the bioactivity of various signaling pathways when in soluble form [293–295]. Moreover, several SLRPs bind TGFβ and bone morphogenetic protein (BMP), and several members of this family inhibit cell growth [296,297].
The crystal structure of bovine decorin [298] shows a solenoid fold structure typical of LRRs (Fig. 5B). Each LRR unit is composed of ~24 amino acids, characterized by a conserved pattern of hydrophobic residues, with short parallel β-sheet on the concave face interwoven with loops containing short β-strands, 3_10 helices and polyproline II helices on the convex (outer) side of the protein core (Fig. 5B). The LRRs form a curved, solenoid structure where protein/protein interactions occur primarily via the side chains of variable residues protruding from the short parallel β-strands that form the inner (concave) face of the solenoid. The LRRs are flanked at the N- and C-termini by disulfide-bonded caps which define the various classes [277]. At the N-terminus, there are four Cys residues with a variable number of intervening amino acids, whereas the C-terminal capping motif encompasses two LRRs and includes the so-called ear repeat (Fig. 5B). This Cys-capping motif, designated LRRCE, is present in the canonical SLRPs (Classes I–III) but absent in the other two non-canonical classes [299]. Likely, both capping motifs at either end of SLRPs Class I–III would function to stabilize the LRR central domain as in the case of other LRR protein and receptors.

Another characteristic feature of Class I–III SLRPs is the presence of a long penultimate LRR (LRR XI in decorin), that has been called the “ear” repeat [300]. Typically, the ear repeats contain 30 or more amino acid residues including an atypical sequence harboring a Cys located at about 10 residues after the asparagine residue in the consensus LRR [300]. Genetic mutations in the decorin gene leading to a terminal truncation of the decorin protein core, lacking the ear repeat, cause congenital stromal corneal dystrophy [301]. This syndrome has been faithfully reproduced in mice where this truncated decorin was specifically expressed into the cornea [302,303].

Although bovine decorin has been crystallized as an anti-parallel dimer [298] and reported to be a dimer in solution [304], there is strong evidence that decorin acts as a monomer in solution [293], especially when interacting with the small binding site on the EGFR ectodomain in vivo where a dimer could not fit the cavity [305]. Also supportive of a concave face binding is the identification of the sequence (SYIRIADTNIT) in LRR VII (highlighted in yellow in Fig. 5B) of the decorin protein core that is directly involved in binding to collagen type I [306,307]. A recent study utilizing mutant forms of mouse decorin, where engineered glycosylated sites in the concave face prevent dimerization, has shown that the monomeric mutants are as stable as the wild-type in solution [308]. The concave face mutants fail to bind collagen, regardless of the dimerization state, thus providing robust biological evidence for a concave face-mediated binding (i.e., monomeric decorin) to collagen [308].

A hallmark shared by nearly all SLRPs, and by most LRR-containing proteins, is their propensity to interact with other proteins and to regulate collagen fibrillogenesis [282,283,309,310]. For example, several SLRPs interact with fibrils of collagen types I, II, III, V, VI and XI. Indeed, the eponym “decorin” derives from its ability to decorate fibrillar (banded) collagen in a periodic fashion, that is, decorin protein core non-covalently binds, about every 67 nm, to an intraperiod site on the surface of collagen fibrils, every D period [311,312]. In highly purified α1(I) procollagen molecules, decorin protein core binds close to an intermolecular cross-linking site near the C terminus [313]. SLRP coating of various
types of collagen serves a dual function: it regulates the lateral association of collagen molecules into proper fibrils, and protects collagen fibrils from proteolysis by sterically limiting the access of collagenases to their cleavage sites. It is important that, during evolution, these dual functional properties of SLRPs are shared by both their sulfated GAGs and protein cores. Notably, few SLRP members contain stretches of amino acids that can be sulfated, such as the poly-Tyr sulfate in fibromodulin or the poly-Asp region in asporin. Often, the GAGs are located in the N-terminus, in a location that is similar to that of these poly-sulfated amino acid stretches, and can be directly involved in collagen interaction [314,315]. An additional degree of complexity is provided by the heterogeneous structure of the GAG chains. For instance, Class I SLRPs contain CS or DS chains, with the exception of asporin, ECM2, and ECMX. In contrast, Class II members contain poly-lactosamine or KS chains in their LRRs and sulfated Tyr residues at their N-termini. Class III members contain CS/DS (epiphycan), KS (osteoglycin), or no GAG (opticin). Finally, the non-canonical Class IV and V members lack GAG chains with the exception of chondroadherin, which is substituted with KS.

The biological functions of SLRPs are very vast and there are over 3000 published papers on decorin alone, the archetypal and most studied SLRP. Thus, we refer the readers to recent comprehensive and specialized reviews on SLRPs [275,281–283,294,307,316–325]. Moreover, it has been proposed that SLRPs can be transcriptionally co-regulated through utilization of HOX-Runx modules in their promoters and genomic regions, including proximal exons and intergenic regions [326]. Below, is a brief overview of each family with emphasis on recent discoveries of their multiple functional roles in physiological and perturbed states.

**Class I SLRP**—Decorin, also known as PG40 and DSPG1, was originally cloned from a fibroblast cDNA library [327], and subsequently named decorin because of its ability to decorate collagen fibrils [328]. Specifically, decorin protein core is a Zn$^{2+}$ metalloprotein [329,330] that is biologically active in solution as a monomer [293]. As mentioned above, decorin protein core binds non-covalently to an intraperiod site on the surface of collagen fibrils about every 67 nm, at the D period [312]. Using purified collagen and procollagen molecules, that can be visualized by their C-terminal globular regions, it has been shown that decorin protein core binds near the C terminus of collagen α1(I), near an intermolecular cross-linking site [313]. Not only the protein core but also the N-terminal GAG chain of decorin plays a role in collagen fibrillogenesis and structure [285,314,315,331–334]. The strategic location of the GAG binding domain in the N-terminus of decorin allows a higher degree of mobility for the DS chain, which presumably could align orthogonally or parallel to the axis of the collagen fibrils. This dual function of decorin could help in maintaining corneal transparency and biomechanical properties of various connective tissues [282,284,335].

The decorin gene exhibits a complex genomic organization and transcriptional control [276,336–338] and its transcription can be induced by quiescence and suppressed by TNFa [339,340]. It was known for many years that the small DSPG of tendon, mostly decorin, is capable of inhibiting lateral growth of collagen fibrils [309]. Thus, when the decorin-null mice were generated, the first targeted deletion of a proteoglycan-encoding gene, the
abnormal collagen structure in the dermis and the skin fragility phenotype [310] provided the first genetic evidence for a regulatory role for the prototype member of SLRP gene family in collagen fibrillogenesis. The phenotype of the decorin deficient mice includes abnormal collagen fibril morphology in the skin and tail tendon, presumably by being less stable during development due to abnormal cross-linking or enhanced susceptibility to collagenase. The prevalent phenotype of the decorin-null mice is skin fragility caused by a thinning of the dermis with concurrent reduced tensile strength, a biomechanical impairment directly linked to the abnormal collagen network. Overall, the $Dcn^{-/-}$ mice resemble the cutaneous defects observed in the Ehlers–Danlos syndrome, characterized by skin hyperextensibility and tissue fragility [341], in a way opposite to fibrosis [342]. Due to its mild phenotype, the $Dcn^{-/-}$ mice have been utilized by a large number of investigators using many experimental challenges and have provided strong genetic evidence for decorin roles in Lyme disease [343,344], lung mechanics and asthma [345,346], diabetic nephropathy and tubulointerstitial fibrosis [347–350], myocardial infarction [351], corneal transparency and tendon biomechanical properties [352–356], dentin mineralization and periodontal homeostasis [357–359], hepatic fibrosis and hepatocellular carcinoma [318,360–362], collagen fibrillogenesis [314,363,364], fetal membrane biology [365–367], wound healing and angiogenesis [368–373], innate immunity and inflammation [291,374,375], adhesion and migration [376], and mesenchymal stem cell biology [377]. Decorin plays an important role during zebrafish development insofar as $zDcn$ knockdown causes a severe phenotype characterized by abnormal convergent extension, craniofacial abnormalities, and cyclopia [278]. As these genetic defects are reminiscent of several zebrafish mutants affecting the non-canonical Wnt signaling pathway, it is possible that decorin might also play a role in this pathway in mammalians. Indeed, a recent study has shown that decorin is directly involved in modulating the signaling pathway of Wnt3a shaping niches supportive of hematopoiesis [378].

Mutations in the decorin gene have been linked to congenital stromal corneal dystrophy (CSCD) syndrome [301,379] where a truncated form of decorin lacking the ear repeat, the C-terminal 33 amino acids, acts in dominant negative fashion. A corneal knock in transgenic mouse lacking the C-terminal 33 amino acid residues (952delTDcn) faithfully recapitulates the human phenotype of corneal opacities [302]. Mechanistically, the C-terminal truncated form of decorin is retained in the cytoplasm of keratinocytes, triggering ER stress and an unfolded protein response [380]. These data provide a cell-based, rather than ECM-based, interpretation of the CSCD phenotype whereby a truncated SLRP protein core, by inducing ER stress, causes an abnormal processing and secretion of decorin and other SLRPs, eventually generating an abnormal matrix assembly and corneal opacities.

Decorin was the first proteoglycan to be directly involved in the control of cell growth. Two seminal papers identified decorin as a growth suppressor, via a mechanism involving decorin’s binding to and inhibiting TGF$\beta$ in Chinese hamster ovary cells [381,382]. Concurrently, decorin was identified as a proteoglycan highly expressed in the tumor stroma of colon carcinomas [383], primarily via hypomethylation of its promoter regions [384]. It was soon recognized, however, that the growth of most malignant cells does not depend on the availability of TGF$\beta$. Thus, there had to be other signaling receptors for the growth suppressive function of decorin. The existence of such receptor(s) was supported by an
emerging body of literature describing that ectopic expression of decorin or its protein core suppress the malignant phenotype in a variety of histogenetic malignant backgrounds [385,386]. Utilizing A431 cells, a squamous carcinoma cell line which overexpress EGFR, it was discovered that exogenous decorin proteoglycan or protein core transiently activated the EGFR to induce growth inhibition via expression of the cyclin-dependent kinase inhibitor p21\textsuperscript{WAF1} [287,387,388]. Indeed, decorin binds to a narrow region of the EGFR, partially overlapping with but distinct from the EGF-binding epitope [305]. Mechanistically, decorin transiently activates the EGFR and elevates cytosolic Ca\textsuperscript{2+} in A431 cells [389], but it causes a sustained down-regulation of this RTK, thereby providing a plausible mechanism for controlling tumor growth \textit{in vivo} in various forms of cancer [390–392]. Specifically, soluble decorin evokes protracted internalization and degradation of the EGFR via caveolar endocytosis [393]. An anti-oncogenic role for decorin has been also demonstrated in its ability to inhibit another member of the ErbB family, namely the ErbB2/Neu, in this case by inhibiting heterodimerization of ErbB4 with ErbB2, thereby leading to growth suppression and cytodifferentiation of mammary carcinoma cells [394]. It was subsequently found that decorin binds specifically and with higher affinity (\(K_D \sim 2\) nM) to hepatocyte growth factor receptor known as Met [288] and causes proteasomal degradation of Myc and \(\beta\)-catenin, two critical downstream effectors of Met [395]. An important downstream effect of the decorin/Met interaction is induction of two anti-angiogenic proteins, Thrombospondin 1 and TIMP3, with concurrent inhibition of two powerful pro-angiogenic factors, HIF-1\(\alpha\) and VEGFA [371,372]. Moreover, decorin binds and suppresses both the IGF-IR [289,396,397] and VEGFR2 [371,398].

Loss of decorin in the tumor stroma correlates with poor survival of patients with invasive breast carcinomas [275,399,400] and in mice with spontaneous breast cancer [401]. Moreover, decorin is markedly reduced in the stroma of many solid tumors [402–404], as well as low- and high-grade bladder carcinomas, but is highly expressed in the normal bladder stroma [397]. Decorin levels are also decreased in multiple myeloma [405,406], soft tissue sarcomas [407], prostatic [408], urothelial [409–411] and hepatic [362,412] carcinomas, together with a complete loss of decorin expression by several tumor cells [413,414]. Additional proof for an oncostatic role of decorin as a soluble tumor repressor stems from genetic models wherein ablation of decorin under conditions of a high-fat, western-type diet, is linked to the spontaneous appearance of intestinal tumors [415,416]. Moreover, compound \(Dcn^{-/-};Tp53^{-/-}\) mice die of aggressive T-cell lymphomas much sooner than mice lacking only the tumor suppressor \(Tp53\) [417]. Notably, systemic delivery of decorin, either as a soluble factor or via adenoviral gene delivery, significantly retards tumorigenic and angiogenic growth in a wide variety of malignant solid tumors [413,418–424]. Collectively, these findings provide strong support to the concept that decorin could act as a “\textit{guardian from the matrix}” in analogy to p53, a guardian of the genome [414]. Thus, decorin could become a potent therapeutic factor, either alone or in combination with traditional chemotherapy, in preventing tumor progression and metastasis [297].

Recently, it was discovered that soluble decorin evokes excessive autophagy in endothelial cells, independently of nutrient deprivation, through partial agonistic activity on VEGFR2 [425]. This signaling cascade emanating from the decorin/VEGFR2 interaction leads to two effects. First, it activates AMPK\(\alpha\) and Vps34, which in turn stimulate the synthesis of Peg3
Biglycan, decorin's closest proteoglycan, was originally isolated from bovine bone and then, following its cloning and sequencing, was found to contain two Ser-Gly attachment sites in the N-terminal region, thus its eponym meaning two GAG chains [431]. Both the human and mouse genes have an overall similar exonic arrangement [432,433]. It is highly homologous to decorin, with > 65% overall homology. Similar to decorin, biglycan binds TGFβ [434] and modulates its bioactivity [435]. Ablation of the biglycan gene, Bgn−/− (this genetic symbol designates the presence of Bgn gene on the X chromosome), which harbors a gene with a ubiquitous tissue distribution and a pronounced expression in bone [433,436], reveals a key function for this SLRP in regulating postnatal skeletal growth [437]. In general, the long bones in Bgn−/− mice grow slower than wild-type littermates and eventually are shorter and exhibit reduced bone mass. The latter is secondary to the marked decline in number of osteoblasts with concurrent progressive depletion of the bone marrow stromal cells [437]. These mutant mice also display delayed osteogenesis after marrow ablation [438], broader metadentin, and altered dentin mineralization, causing significant enamel structural defects. Thus, biglycan-deficient mice could be a promising animal model to study skeletal diseases and osteoporosis [439]. Although Dcn−/− mice also show abnormalities in bone collagen fibril size and organization, they show neither overt bone mass defects nor abnormal osteoblast growth as in the case of biglycan deficiency. These findings underline non-overlapping functions that have evolved for these two homologous Class I SLRPs.

Biglycan modulates BMP-4-induced osteoblast differentiation [440], and it also binds Chordin and BMP-4 in Xenopus embryos, thereby blocking BMP-4 activity [441]. Moreover, biglycan affects the Wnt signaling pathway [442], in analogy to decorin (see above). However, a recent study has shown that biglycan acts as a pro-angiogenic stimulus in contrast to decorin, suggesting that these two functions are SLRP-specific. This pro-angiogenic activity of biglycan is mediated by its binding to VEGFA and its potentiation of the VEGFR2 signaling pathway [443]. This bioactivity favors fracture healing via a pro-angiogenic stimulus, a process that is markedly attenuated in the absence of biglycan [443]. Biglycan can also affect cell growth by inducing the cyclin-dependent kinase inhibitor p27KIP1 in pancreatic carcinoma cells [444], as well as myofibroblast differentiation and proliferation by modulating the TGFβ/Smad2 signaling pathway [445].

A significant paradigmatic shift for biglycan biology was the discovery that this SLRP is proinflammatory and binds to Toll-like receptors (TLR)-2 and -4 [446]. The key observation again came from genetic studies where biglycan-deficient mice show a greater survival rate
than wild-type when subjected to lethal LPS-induced sepsis. Mechanistically, biglycan is highly produced and secreted by circulating macrophages, thereby acting as a danger signaling molecule for the innate immunity receptors TLR-2/4 [446] and by activating the inflammasome via TLR-2/4 and the purinergic P2X receptors [447]. Indeed, biglycan-evoked TLR-2/4 activation exacerbates the outcome of ischemic acute renal injury [448] and induces the synthesis and secretion of several chemo-attractants in the kidney, thereby enhancing the inflammatory damage [449]. Some of the pro-inflammatory roles of biglycan affect the pulmonary parenchyma as well via a receptor cross-talk [323,450]. Recently, it has been proposed that biglycan could act as a biomarker of inflammatory renal diseases [451]. Thus, an emerging picture is appearing where biglycan, often in contrast to its “first cousin” decorin, links the innate to the adaptive immunity, thereby operating in a broad biological environment including microbial and non-microbial pathogenesis, and cancer growth and inflammation [452].

Another Class I SLRP is asporin, also known as PLAP-1 or periodontal ligament-associated protein 1. Asporin was originally isolated from cartilage extracts of human patients with early osteoarthritis and was soon recognized to share homology with other SLRP members [453]. Its eponym derives from the N-terminal region enriched in aspartic acid and its homology to decorin. Asporin, although being similar to decorin and biglycan in its overall structure, does not contain Ser-Gly dipeptides capable of GAG substitution; thus it might not have GAG chains [454]. The overall tissue distribution of asporin is similar to that of decorin [276], with high expression detected in the skeleton and other mineralized connective tissues, but with minimal expression detected in all parenchymal organs [454]. Asporin is located on human chromosome 9 and is a member of the chromosomal SLRP gene cluster that includes osteoadherin, osteoglycin and ECM2. The N-terminal polyaspartate domain binds calcium and regulates hydroxyapatite formation [455]. Moreover, asporin and decorin compete for binding to collagen via LRR10–12, and asporin’s role in biomineralization is further corroborated by its expression in osteoblast progenitor cells [456], key players in intramembranous bone formation. Asporin antagonizes chondrogenesis in articular cartilage by interfering with the TGFβ1/receptor interaction on the cell surface and by inhibiting the canonical TGFβ/Smad signaling pathway [457]. Specifically, suppression of ASPN gene expression via siRNA leads to increased expression of TGFβ1 [457], which in turn stimulates the expression of asporin indirectly via upregulation of Smad3 [456]. In agreement with these concepts is the discovery that a polymorphism in the polyaspartate region of asporin (D14 allele) is strongly associated with osteoarthritis. Moreover, the frequency of the D14 allele increases with disease severity [458]. Asporin is expressed at high levels in the more degenerate human intervertebral discs [459]. Moreover, asporin suppresses the TGFβ-evoked expression of aggrecan and collagen type II and reduces proteoglycan accumulation in an in vitro model of chondrogenesis, again both prominently linked to the D14 allele [458]. Thus, asporin and TGFβ1 form a regulatory feedback loop to fine tune chondrogenesis. Recently it has been reported that asporin is highly expressed in the cancer-associated fibroblasts of scirrhous gastric carcinomas [460]. In this case, asporin promotes invasion by neighboring cells in a paracrine fashion by activating the CD44-Rac1 pathway [460].
Finally, ECM2 and ECMX, two poorly-studied SLRP Class I, are two genes that are related to decorin, being ~35% homologous to the LRR of decorin. However, both SLRPs have a larger size and contain an RGD sequence known to bind integrin receptors and a von Willebrand Factor-like domain [461]. ECM2 is predominantly expressed in adipose tissue and in female organs such as mammary gland, ovary and uterus [461]. Interestingly, ECM2 gene is physically linked to asporin on chromosome 9, and its promoter shares cis-acting elements in common with other members of SLRP gene family [326]. These SLRPs are included in Class I based on genomic and protein homology, although most likely they do not contain any GAG chains. Future studies are needed to decipher their biological function.

Class II SLRP—This class includes five SLRPs that can be further subdivided into three subgroups based on protein homology. Subgroup A includes fibromodulin and lumican, subgroup B harbors PRELP and keratocan, and subgroup C includes osteoadherin. All these Class II SLRPs have homologous genomic organization (three exons), with the largest exon encoding for most of the LRRs. All contain a charged N-terminus with multiple tyrosine sulfate residues that contribute to the anionic properties of these proteoglycans. Characteristically, Class II SLRPs are substituted with keratan sulfate and polylactosamine, an unsulfated variant of KS. Notably, corneal KS binds with high affinity to FGF2 and sonic hedgehog [462], indicating that KSPGs can participate in the modulation of growth factor activity and morphogen gradient formation. Many of these SLRPs are highly expressed in connective tissues and cartilage where they bind many ECM constituents, especially fibrillar collagens, thereby stabilizing the fibrillar network that constitutes the framework of the tissue [242]. KSPGs are also directly involved in regulating corneal transparency, especially the interfibrillar spacing of orthogonal fibers, and their sulfation pattern is highly conserved throughout the cornea [463].

Fibromodulin was originally isolated from cartilage [464] and soon realized to be homologous to decorin. Its eponym derives from the fact that fibromodulin binds to collagens I and II and causes delayed fibril formation [465,466]. The N-terminus of fibromodulin contains a stretch of tyrosine sulfate residues which can be cleaved by MMP-13 [467]. As fibromodulin N-terminal domain appears to be exposed following its binding to fibrillar collagens, it is possible that this charged domain would have a dual function: it could be involved in collagen cross-linking and it could bind and sequester growth factors such as members of the FGF and VEGF family, as well as several inflammatory cytokines released during tissue remodeling. Indeed, this domain, as that of osteoadherin (see below), physically interacts with basic clusters of several heparin-binding growth factors and cytokines [468]. Fibromodulin is a major KSPG [469] and some molecules contain KS chains exclusively capped with α(2–3)-linked sialic acid [470]. It regulates collagen fibrillogenesis during corneal development [471]. Fibromodulin binds to same region of collagen I where lumican binds [472], but in a region different from the decorin binding site [473]. Specifically, fibromodulin binds collagen I via residues located in LRR11, between Glu-353 and Lys-355, located in the convex surface of the protein core [474]. In contrast, both lumican and fibromodulin bind to collagen I via a more proximal region located between LRR5 and LRR7 [475]. In spite of this overlapping binding, it has been reported that differential expression of lumican and fibromodulin regulates collagen
Fibrillogenesis during mammalian tendon development [476]. Thus, there is redundancy and specificity for SLRP binding and modulation of collagen fibrillogenesis in vivo. As other SLRPs, fibromodulin binds TGF-β [434], and, in common to decorin [477], binds the collagenous part of complement C1q [478]. However, and in contrast to decorin, fibromodulin activates the classical complement pathway [478].

Fibromodulin is widely distributed in connective tissues, and, thus, the phenotype of Fmod−/− mice is quite complex [479,480]. These mutant mice exhibit abnormal collagen fibril organization, but they also show abnormal deposition of lumican in tendon [481], and abnormal dentin mineralization [482] and alveolar bone formation [483,484]. The phenotype of Fmod−/− mice becomes ever more complex when these mutant mice are crossed with mice deficient in either biglycan or lumican. Double mutant Lmr+/−;Fmod−/− mice develop a syndrome of joint laxity and tendinopathy [485] reminiscent of patients with Ehlers-Danlos syndrome. Moreover, Lmr−/−;Fmod−/− mice exhibit ocular features of high myopia, including thin sclera and increased axial length [486]. When Fmod−/− mice are mated to homozygosity with Bgn−/0 mice, the double mutants develop ectopic ossification and osteoarthritis [487], and also an accelerated temporomandibular osteoarthritis [488]. In the latter case, osteoarthritis arises from accelerated chondrogenesis secondary to decreased levels of sequestered TGF-β1 in the double mutant Bgn−/0;Fmod−/− mice, thereby causing an over-activation of the TGF-β signaling pathway [488]. This mechanism is similar to that recently reported for excessive TGF-β signaling due to low decorin expression/levels in osteogenesis imperfecta [489] and recessive dystrophic epidermolysis bullosa [490]. In both diseases, the clinical severity of the relative phenotypes is markedly enhanced by TGF-β freed from sequestration by low SLRP levels. Thus, there is a genetic interaction among various SLRPs and their temporal and spatial expression needs to be maintained and finely balanced to prevent significant pathology.

In solid tumors, fibromodulin appears to modulate the tumor stroma by increasing extracellular fluid volume and lowering interstitial fluid pressure [491]. This bioactivity has been proposed to influence cancer fluid balance, which in turn affects the response to chemotherapy [491]. Finally, recent reports have shown that fibromodulin promotes in vitro and in vivo angiogenesis [492], and this is particularly prominent in melanocyte-secreted fibromodulin [493]. Mechanistically, fibromodulin appears to be secreted at high levels in low pigmented melanocytes and it stimulates the secretion of monocyte chemotactic protein-1, which is a powerful angiogenic factor [494].

The second member of Class II SLRP is lumican which was originally characterized from avian cornea as a KSPG and derives its eponym in recognition of lumican’s role in regulating corneal transparency [495,496]. However, it is now clear that lumican is ubiquitously expressed and is localized primarily to mesenchymal tissues and tumor stroma [480,497]. This KSPG plays a critical role in corneal clarity by maintaining the interfibrillar space of the corneal collagen architecture vital for transparency. Indeed, Lmr−/− mice develop bilateral corneal opacities together with skin laxity and fragility reminiscent of Ehlers Danlos syndrome [498]. The posterior corneal stroma is most vulnerable to lumican deficiency as this region shows early developmental defects in fibril structure and architecture in the Lmr−/− mice [499]. The causative role of lumican in corneal opacity is
demonstrated by genetic studies where a mouse overexpressing lumican in the cornea, driven by the keratocan promoter, can fully rescue the Lum\(^{-/-}\) eye phenotype [500]. Notably, these ocular abnormalities are more exaggerated and include scleral alterations when both lumican and fibromodulin are ablated [486]. In zebrafish, knock-down of lumican leads to scleral thinning and increased size of scleral coats [501]. Moreover, mice deficient in lumican and fibromodulin have joint laxity and severe tendinopathy [485]. Indeed, differential expression of lumican and fibromodulin (see above) regulates the proper alignment and overall structure of collagen fibrils during murine tendon development [476,502].

Lumican has been involved in cancer and inflammation [503], two areas of research where other SLRPs, predominantly Class I decorin and biglycan, have been extensively investigated. One of the first observations was that lumican could inhibit colony formation in soft agar induced by v-K-ras and v-src [504]. Indeed, lumican is markedly increased in the stroma of breast carcinomas [505,506], and is highly expressed in melanomas [507,508]. Lumican also inhibits melanoma progression [509,510], and blocks melanoma cell adhesion via interaction with \(\beta_1\)-containing integrins [511] and by modulating focal adhesion complexes [512]. These effects are all mediated by the protein core, as a peptide fragment named lumcorin from LRR\(_9\) can by itself inhibit melanoma cell migration [513]. Lumican has also been involved in other forms of malignancy including prostate cancer [514], pancreatic cancer [515], and osteosarcomas [516]. In the latter case, lumican regulates osteosarcoma cell adhesion by modulating TGF\(\beta\)2 activity [517]. Lumican can be the target of MMPs and can also inhibit MMP activity, as recently shown for MMP-14 [518]. Using expression cloning, it was found that lumican specifically interacts with membrane-type MMP-1, which can cleave lumican, thereby preventing induction of p21 [519], with a mechanism similar to the p21 induction described for decorin [387]. Thus, it seems that in certain neoplastic conditions the biological effects of Class I and II SLRPs can converge on an antioncostatic function, as decorin was also found to be susceptible to membrane-type MMP-1 cleavage in the same cell system [519].

Lumican’s involvement in inflammation is exemplified by the findings that lumican regulates corneal inflammation by binding to the Fas ligand and thus interfering with Fas–Fas ligand interaction [520]. This mechanism is again shared by Class I SLRPs where several components bind various forms of TGF\(\beta\). Notably, lumican deposited on the surface of neutrophils during their transmigration across endothelia promotes neutrophil migration via \(\beta_2\) integrin [521] and keratinocyte-derived CXCL1 chemokine [522]. These findings are consistent with a role for lumican in evoking neutrophil recruitment and invasion following corneal injury and wound healing [523]. Lumican can also interact with the innate immune receptor Toll-like receptor 4 [524], as it was previously shown for the Class I SLRP biglycan [446]. Soluble lumican evokes bacterial phagocytosis thus providing a molecular protection against Gram-negative bacteria [525]. This biological function of lumican has been corroborated by genetic studies whereby Lum\(^{-/-}\) mice show an enhanced pulmonary infection by *Pseudomonas aeruginosa* [525] and a low innate immunity and inflammatory response in a murine model of colitis [526]. Recently, it has been shown that lumican binds via its C-terminal 50 amino acid region to TGF\(\beta\) receptor 1, also known as ALK5 [527].
Thus, in common to other SLRP members, lumican can affect both the innate immune system and the TGFβ signaling pathway.

PRELP (proline/arginine-rich end leucine-rich repeat protein), also known as prolargin, derives its eponym from its unique N-terminal domain enriched in basic amino acid residues [528]. The N-terminus of PRELP binds heparin, heparan sulfate and also tyrosine sulfate-rich domains of Class III SLRPs, fibromodulin and osteoadherin [242]. PRELP was originally isolated from cartilage extracts and found to be expressed predominantly in the territorial matrix [464]. However, it is now recognized that PRELP has a much wider distribution, with expression in kidneys, aorta, liver and skeletal muscle. It is expressed in pericellular regions near basement membranes [242]. Indeed, PRELP binds to the N-terminus of perlecan via its HS chains and thus it might constitute a bridge between basement membranes and the surrounding collagenous matrices linked by the LRRs of PRELP [529]. Notably, the N-terminal positively-charged domain of PRELP inhibits NF-κB signaling and thus acts as a potent anti-resorptive molecule attenuating osteoclast formation [530]. A peptide derived from the N-terminus of PRELP has been recently shown to concurrently inhibit the progression of osteoporosis and the formation of osteolytic bone metastases from aggressive mammary carcinoma xenografts [531].

Another biological function of PRELP is its ability to inhibit the formation of complement membrane attack complex [534]. Thus, PRELP could suppress complement attack near basement membranes of vascularized tissues and diminish pathological complement activation in chronic inflammatory disease such as rheumatoid arthritis [534]. Recently, this bioactivity of PRELP has been exploited in murine models of macular degeneration, where AAV-mediated delivery of human PRELP inhibits complement activation, choroid angiogenesis and deposition of the membrane attack complex [535].

Another Class II SLRP member is keratocan, a KSPG involved in maintaining corneal transparency [536,537]. It contains three chains of KS, a highly-sulfated linear polymer of N-acetyl-lactosamine covalently linked to asparagine residues via a mannose-containing oligosaccharide. Mice deficient in keratocan, Kera−/−, have normal corneal transparency, but they exhibit a thinner corneal stroma and a narrow corneal/iris angle vis-à-vis wild type littermates [538]. Moreover, Kera−/− corneas have larger collagen fibrils and abnormal packing of the stromal collagen, indicating a role for keratocan in maintaining proper corneal structure [538]. Consistent with a role for keratocan in corneal physiology, KERA mutations in a Finnish population have been causatively linked to a severe form of cornea plana, the autosomal recessive cornea plana (CNA2) [539]. The key observation, which now extends to other non-Finnish populations [540], is that these affected patients have recessively inherited N247s mutation that replaces a single asparagine residue in the LRRR consensus sequence. This leads to loss-of-function of keratocan. Noticeably, another mutation Q174X leads to a truncated form of keratocan and this is also linked to CNA2 [539]. Keratocan is expressed in organs other than the ocular system, especially prominent being skin, tendon, cartilage and striated muscle [536,537,541]. It is also expressed in osteoblasts and it might be involved in osteogenesis since Kera−/− show a decreased rate of
bone formation and mineral apposition [542]. Keratocan fragments, together with fragments of other SLRPs (decorin, biglycan and lumican) are increased in degenerate human menisci, knees and articular cartilages [543]. As in the case of lumican, keratocan contains short, non-sulfated poly lactosamine chains in tissues other than cornea [536], suggesting that they might serve other functions in non-ocular systems. In addition to its structural role, this KSPG is involved in regulating corneal inflammation by actively binding the major neutrophil chemokine CXCL1/KC and forming a chemokine gradient that evokes neutrophil recruitment [522]. Moreover, keratocan and lumican play a role in resolution of the inflammatory response, as neutrophils are required for cleavage of these KSPGs and release of cleavage products and chemokines are detected in the anterior chamber, resulting in loss of the chemokine gradient and cessation of neutrophil infiltration [544].

Osteoadherin, also known as osteomodulin, was originally isolated from guanidinium extracts of bovine bone as a cell-binding KSPG, hence its eponym [545]. It is highly expressed in mineralized tissues reaching concentrations of up to 400 µg/g wet weight, where it localizes to the primary spongiosa of fetal growth plate [545]. Osteoadherin contains six closely-spaced tyrosine sulfate residues in its N-terminal extension and two in its C-terminal region [546]. The N-terminal domain also contains a large number of acidic amino acid residues that, together with the tyrosine sulfate ones, would generate a strong polyanionic scaffold [547]. This region could simulate “heparin” in several interactions with growth factors and cell surfaces [242]. Indeed the tyrosine sulfate-rich domains of both fibromodulin and osteoadherin bind basic cluster motifs shared by a wide variety of heparin-binding proteins and growth factors [468]. The ability of osteoadherin to provide a cell-binding substrate is shown by the fact that this KSPG is as efficient as fibronectin in promoting osteoblast attachment in vitro [545]. The binding is mediated by the αvβ3 integrin, as shown by osteoadherin-linked affinity chromatography [545]. During endochondral bone formation, the glycosylation pattern of osteoadherin is quite unique. It is primarily a KSPG in the mineralized zone of developing bones, but it is unglycanated in the non-mineralized zones [548], further reinforcing a role for this KSPG in endochondral bone mineralization [548]. Osteoadherin, together with biglycan, decorin and fibromodulin, is dynamically expressed during odontogenesis [358,549]. Osteoadherin is primarily localized in the predentin, generating a gradient toward the mineralization front suggesting a direct role in regulating tooth development [549].

**Class III SLRP—** This class encompasses three structurally and genomically related members, epiphycan, opticin and osteoglycin. This class contains only seven LRRs in contrast to the more usual 10–12 LRRs of the other classes. In common with Class II members, Class III members harbor N-terminal consensus sequences for tyrosine sulfation, which may provide am signal for keratan sulfate addition to the protein core during assembly and post-translational modification [536].

Epiphycan was originally isolated as a glycoprotein from the epiphyseal cartilage, and thus its eponym [550]. It was soon realized that epiphycan is the mammalian ortholog of the avian dermatan sulfate proteoglycan PG-Lb, isolated from the developing chick cartilage, with Lb standing for its low buoyant density during its purification using density gradient ultracentrifugation [551]. Epiphycan has a precise spatiotemporal distribution during
cartilage development and is localized to the entire growth plate, suggesting that epiphycan is a player in chondrogenesis [552]. Although the Epyc−/− mice have a mild bone phenotype, the epiphycan/biglycan double-knockout mice have shorter long bones and developed osteoarthritis with age, suggesting a potential synergism between these two SLRPs [553]. Notably, epiphycan has recently been shown to be part of collagen IX interactome, further suggesting that it might be involved in growth plate organization [554].

Opticin was concurrently isolated and characterized by several groups and has also been named oculoglycan [555–557]. The eponym obviously derives from its original ocular source of cloning/purification, although its expression is not limited to the eye. Several opticin ESTs are present in many data banks from nonocular tissues including brain, kidney, urinary bladder and uterus. Indeed, opticin is also expressed in the human articular cartilage and it’s degraded in osteoarthritis by MMP-13 [558]. In contrast, in the mouse opticin appears to be localized to the eye, especially in the ciliary body [325]. More recently, opticin has been identified as one of the tyrosine sulfated constituents of the retinal pigment epithelium [559]. In common with Class I member decorin [369,371], opticin inhibits angiogenesis [560] by binding to collagen and competitively disrupting the interaction of collagen with α1β1 and α2β1 integrins, two key receptors regulating experimental and developmental angiogenesis [194,561–564].

Osteoglycin, also known as mimecan, was originally isolated as a truncated protein from bone and later identified as a keratan sulfate SLRP in the cornea [565,566]. Numerous mRNA are generated from a single Ogn gene, and these mRNA are all detectable in the cornea, although a single protein core is generated [326,567,568]. Functionally, Ogn−/− mice have increased collagen fibril diameter in both cornea and dermis [569], analogous to other SLRP phenotypes described above. These studies have been corroborated by the observation that both osteoglycin and epiphycan appear to be proteolytically processed in vivo. Specifically, osteoglycin is processed by BMP-1/Tolloid-like metalloproteinases and this processing enhances osteoglycin’s ability to regulate collagen fibrillogenesis [570].

One of the emerging biological roles of osteoglycin is its ability to modulate myocardial integrity and injury, and to affect cardiac remodeling in concert with several ECM glycoproteins of the myocardium [571]. An integrated genomic approach has found that elevated osteoglycin is a positive regulator of rat left ventricular cardiac mass, and OGN transcript abundance has the highest correlation with left ventricular mass among 22,000 subjects tested [572]. In support of these observations is the finding that abnormal collagen assembly in Ogn−/− mice leads to increased infarct rupture and wall thinning after myocardial infarction, and this phenotype can be improved by adenoviral-mediated Ogn gene delivery [573]. Of interest, and in analogy to decorin and biglycan which are also increased in the circulation following inflammation and cancer, circulating osteoglycin levels are markedly increased in patients with ischemic heart failure and correlate with markers of cardiac remodeling [573]. Recently, it has been shown that osteoglycin can act as anabolic bone factor secreted by muscle cells [574], and that increased levels of circulating osteoglycin correlate with vascular remodeling in apolipoprotein E-deficient mice [575]. Thus, osteoadherin or fragment of it could act as predictors of adverse cardiovascular events after coronary angiography [576]. Thus, as in the case of decorin and biglycan, several other
SLRPs are found in the circulation, and, hopefully in the near future, we will dissect their function as key components of the human plasma.

**Class IV SLRP**—This non-canonical class of SLRPs includes chondroadherin [577], nyctalopin [578,579] and tsukushi [580].

Chondroadherin is primarily located in cartilage and provides a link between chondrocytes and the surrounding ECM via specific interactions with the α2β1 integrin [581] and HS chains [582]. As perlecan also binds to the same integrin [168] and it contains HS chains at its N-terminus, it is possible that chondroadherin and perlecan could compete for the same binding site, especially when perlecan has been shown to be arranged in a peri-chondrocytic basement membrane-like zone [583]. Chondroadherin also binds to collagens II and VI and Chad−/− mice show both cartilage and bone abnormalities [584]. A recent study using atomic force microscopy has shown that the Chad−/− cartilage show abnormal collagen network assembly and mechanical properties especially in the superficial cartilage zone [585].

Nyctalopin is a quite interesting and unique SLRP for two reasons: (a) It is the only member of this family that is GPI-anchored to plasma membrane, and (b) It is the only SLRP gene member, with the exception of biglycan, to be located on the X chromosome. Several mutations in the NYX gene have been causatively linked to X-linked congenital stationary blindness, a group of retinal diseases characterized by reduced nocturnal vision, often associated with myopia and reduced visual acuity [578,579]. Notably, mutations in the TRPM1 gene (transient receptor potential cation channel subfamily member 1) are associated with congenital stationary blindness [586]. It is interesting that in the mouse eye, nyctalopin is a transmembrane SLRP rather than anchored via GPI [587]. Thus, it seems that the mode of anchor to the plasma membrane is not important, rather the orientation of this SLRP and its exposed LRR interacting with other receptors and surface proteins. Indeed, nyctalopin interacts directly with both TRPM1 [588,589] and the glutamate receptor mGluR6 [589]. Thus, it is likely that nyctalopin is a key component of a supramolecular complex, where this SLRP acts as scaffold to target and maintain the correct signaling ensemble at the visual synapse.

The final Class IV SLRP member is tsukushi, an eponym derived from its expression pattern in avian embryos reminiscent of the Japanese horsetail plant tsukushi (*Equisetum arvense*) [580]. Tsukushi has important regulatory functions insofar as it is involved in modulating BMP and Wnt signaling pathways [580,590–593]. For example, overexpression of tsukushi in embryonic retinal cells, both in vivo and in vitro, effectively antagonizes Wnt2b and represses Wnt-dependent specification of peripheral eye fates [593]. Moreover, tsukushi binds TGFβ1 [594] and controls macrophage function by inhibiting TGFβ1 [595]. Notably, targeted inactivation of the Tsk gene in mice causes malformation of the corpus callosum, similar to the SPOCK1 mutants [596] (see below) and agenesis of the anterior commissure [597]. This forebrain commissure formation is co-regulated by draxin, dorsal inhibitory axon guidance protein [598]. Finally, tsukushi has been shown to control the hair cycles by regulating the TGFβ1/Smad pathway [594]. Tsukushi shares several functional properties with other SLRPs such as decorin and biglycan, which have been shown to bind TGFβ1 and
modulate BMP and Wnt pathways [278,367,378,442,599–602], as well as controlling the hair follicle cycle [603].

**Class V SLRP**—This is the least studied family of non-canonical SLRPs with only two members, podocan [604,605] and podocan-like [606]. The eponym derives from its high expression in podocytes isolated from sclerotic glomeruli of experimental HIV-associated nephropathy [604]. In normal kidneys, podocan shows a distribution along the basement membrane of the glomeruli and proximal tubules [604], and more recent studies have shown that podocan is a constituent of human aortic tissue [607]. In agreement with its tissue distribution, podocan has been identified as a negative regulator of migration and proliferation of smooth muscle cells [608]. On this basis, podocan can affect atherosclerosis development like other SLRPs, such as biglycan. Of note, Podn−/− smooth muscle cells exhibit a constitutively-activated Wnt pathway, whereas wild-type smooth muscle cells overexpressing podocan have a significantly depressed Wnt signaling pathway [608], biological properties also shared by other SLRPs (see above). As in the case of other-non canonical SLRPs, podocan shares functional properties with decorin and biglycan, especially in its ability to bind collagen I and to induce p21WAF1 and growth suppression [605].

**Testican/SPOCK family**

The next subclass of extracellular proteoglycans includes the testican/SPOCK family of genes. Testican was originally isolated from seminal fluid over two decades ago as a hybrid CS/HSPG [609] and its sequence showed homology to SPARC, secreted protein acidic and rich in cysteine, also known as BMP-40 [610]. The testican family of HSPGs has now been shown to comprise three members and has been renamed SPOCK, referring to SPARC/Osteonectin CWCV and Kazal-like domain proteoglycans [611–614]. SPOCKs have a modular structure, similar to perlecan and agrin, characterized by five domains (Fig. 6). Domain I, a SPOCK-specific N-terminal domain, does not have any significant homology except to other members of the testican/SPOCK proteoglycan gene family. Domain II is a cysteine-rich module homologous to follistatin, also shared by agrin (cfr. Fig. 1). Domain III shares homology with the extracellular calcium-binding domain of SPARC, characterized by two Ca2+-binding EF-hand motifs [615]. Domain IV harbors a thyroglobulin-like domain, relatively short sequence stabilized by three disulfide bonds and harboring a CWCV tetrapeptide sequence [612]. The C-terminal Domain V, in analogy to Domain I, is unique to the testican/SPOCK family and harbors two potential GAG attachment sites [616]. Notably, SPOCK3 contains two consecutive SGD triplets, known attachment sites for HS also shared by perlecan and agrin. Although isolated from testis, it has become apparent that SPOCKs are almost exclusively expressed in the central nervous system and they are primarily HSPGs. For example, SPOCK1 is associated with the postsynaptic area of the hippocampus pyramidal cells [617], while SPOCK2 has been located to various neuronal cells of several brain regions including the corpus callosum, cerebral peduncles and fimbria fornix [612]. SPOCK3 is an HSPG in brain and appears to be ubiquitously expressed in the cerebral nervous system, including the forebrain, the striatum, the thalamus and to a lesser extent the cortex [616]. Notably, SPOCK3 and MMP-16 can be co-induced by TGFβ-evoked...
upregulation of a specific MKL1 isoform, a cofactor for the transcriptional program regulated by serum responsive elements [618].

Functional studies utilizing recombinant SPOCK-2 proteoglycan and protein core have shown that both forms inhibit neurite extension from cerebellar neurons, thus providing strong support to the notion that SPOCKs are involved in neuronal regulation [619]. In support of these studies, Spock3−/− mice show many structural anomalies of the corpus callosum and cortical axonal tracts linked to abnormal behavior, supporting a role for SPOCK3 gene in neuronal tropism [596]. A novel de novo missense mutation in SPOCK1 on chromosome 5q31 (c.239A>T; p.D80V), has been recently shown to cause a syndrome including intellectual disability with dyspraxia, dysarthria, partial agenesis of corpus callosum, prenatal-onset microcephaly and atrial septal defect [620]. As this mutation, i.e. replacement of a polar aspartic acid with a hydrophobic nonpolar valine, affects a highly-conserved area of the gene, it is plausible that an abnormal SPOCK1 could contribute to this human phenotype of developmental delay and microcephaly.

**Other proteoglycans**

There are a number of part-time proteoglycans that are not included in this comprehensive nomenclature, including Prg4/lubricin, endocan, leprecan, collagens IX and XII, bikunin and CD44. These molecules have been investigated to a lesser extent and reports are scarce regarding their biological functions as proteoglycans. We do apologize to the authors working on these interesting molecules and we hope to cover them in future updates of this nomenclature.

**Final considerations**

Of the 43 genes encoding full-time proteoglycans, only 33 appear to be glycanated. Thus, roughly 1 in 10,000 genes in the human genome codes for a proteoglycan protein core. This is quite amazing and indicates that proteoglycans play fundamental and often vital functions necessary for life to operate and evolve. We are confident that new proteoglycans will be discovered in the future. One of the major difficulties in finding new proteoglycans is their large size and negative charge. Both hinder proper separation in conventional acrylamide or 2D gels used for routine proteomic studies of various biological fluids and tissues. However, as in the case of agrin and collagen XVIII which were studied for several years without knowing their proteoglycan nature, it is likely that there will be significant discoveries of known proteins as being members of the “restricted” proteoglycan gene family. We hope that this nomenclature will help researchers who want to familiarize themselves with our exciting and growing field of proteoglycan biology.

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## Abbreviations used

| Abbreviation | Description |
|--------------|-------------|
| SLRP         | small leucine-rich proteoglycan |
| LRR          | leucine-rich repeat |
| RTK          | receptor tyrosine kinase |
| GAG          | glycosaminoglycan |
| HS           | heparan sulfate |
| HSPG         | heparan sulfate proteoglycan |
| He           | heparin |
| CS           | chondroitin sulfate |
| KS           | keratan sulfate |
| CSPG         | chondroitin sulfate proteoglycan |
| DSPG         | dermatan sulfate proteoglycan |
| CSPG4/NG2    | chondroitin sulfate proteoglycan 4/nerve glial antigen 2 |
| TGFβ         | transforming growth factor β |
| EGF          | epidermal growth factor |
| EGFR         | EGFR receptor |
| FGF          | fibroblast growth factor |
| VEGF         | vascular endothelial growth factor |
| PDGF         | platelet-derived growth factor |
| BMP          | bone morphogenetic protein |
| PKC          | protein kinase C |
| ZP-C         | zona pellucida C region |
| N-CAM        | neural cell-adhesion molecule |
| RTPT         | receptor-type protein tyrosine phosphatase |
| GPI          | glycosylphosphatidylinositol |
| Hh           | hedgehog |
| Wnt          | wingless-related integration site |
| IGF-II       | insulin-like growth factor II |
| SEA          | sea urchin sperm protein, enterokinase and agrin |
| AChR         | acetylcholine receptor |
| MMP          | matrix metalloproteinase |
| Hyalectan    | hyaluronan- and lectin-binding proteoglycan |
CRP complement regulatory protein
MMP matrix metalloproteinase
ADAMTS a disintegrin and metalloproteinase with thrombospondin motifs
SLRP small leucine-rich proteoglycan
PRELP proline/arginine-rich end leucine-rich repeat protein
SPOCK secreted protein acidic and rich in cysteine (SPARC)/Osteonectin CWCV and Kazal-like domain proteoglycan
TLR Toll-like receptor
LPS lipopolysaccharide endotoxin
CSCD congenital stromal corneal dystrophy
HAT histone acetyl transferase
HDAC histone deacetylase

References

1. Iozzo RV, Murdoch AD. Proteoglycans of the extracellular environment: clues from the gene and protein side offer novel perspectives in molecular diversity and function. FASEB J. 1996; 10:598–614. [PubMed: 8621059]
2. Iozzo RV. Matrix proteoglycans: from molecular design to cellular function. Annu Rev Biochem. 1998; 67:609–652. [PubMed: 9759499]
3. Le BV, Kim H, Choi J, Kim J-H, Hahn M-J, Lee C, et al. Crystal structure of the LG3 domain of endorepellin, an angiogenesis inhibitor. J Mol Biol. 2011; 414:231–242. [PubMed: 21996443]
4. Couchman JR. Transmembrane signaling proteoglycans. Annu Rev Cell Dev Biol. 2010; 26:89–114. [PubMed: 20565253]
5. Sarrazin S, Lamanna WC, Esko JD. Heparan sulfate proteoglycans. Cold Spring Harb Perspect Biol. 2011; 3:1–33.
6. Thacker BE, Xu D, Lawrence R, Esko JD. Heparan sulfate 3-O-sulfation: a rare modification in search of a function. Matrix Biol. 2014; 35:60–72. [PubMed: 24361527]
7. Peysselon F, Ricard-Blum S. Heparin–protein interactions: from affinity and kinetics to biological roles. Application to an interaction network regulating angiogenesis. Matrix Biol. 2014; 35:73–81. [PubMed: 24246365]
8. Zhang X, Wang B, Li JP. Implications of heparan sulfate and heparanase in neuroinflammation. Matrix Biol. 2014; 35:174–181. [PubMed: 24398134]
9. Parish CR, Freeman C, Ziolkowski AF, He YQ, Sutcliffe EL, Zafar A, et al. Unexpected new roles for heparanase in Type 1 diabetes and immune gene regulation. Matrix Biol. 2013; 32:228–233. [PubMed: 23499527]
10. Vlodavsky I, Blich M, Li JP, Sanderson RD, Ilan N. Involvement of heparanase in atherosclerosis and other vessel wall pathologies. Matrix Biol. 2013; 32:241–251. [PubMed: 23499530]
11. Vlodavsky I, Iozzo RV, Sanderson RD. Heparanase: multiple functions in inflammation, diabetes and atherosclerosis. Matrix Biol. 2013; 32:220–222. [PubMed: 23499526]
12. Peterson SB, Liu J. Multi-faceted substrate specificity of heparanase. Matrix Biol. 2013; 32:223–227. [PubMed: 23499529]
13. Goldberg R, Meirovitz A, Hirshoren N, Bulvik R, Binder A, Rubinstein AM, et al. Versatile role of heparanase in inflammation. Matrix Biol. 2013; 32:234–240. [PubMed: 23499528]
14. Knelson EH, Nee JC, Bloge GC. Heparan sulfate signaling in cancer. Trends Biochem Sci. 2014; 39:277–288. [PubMed: 24755488]
15. Theocharis AD, Gialeli C, Bouri P, Giannopoulou E, Skandalis SS, Aletras AJ, et al. Cell–matrix interactions: focus on proteoglycan–proteinase interplay and pharmacological targeting in cancer. FEBS J. 2014; 281:5023–5042. [PubMed: 25333340]
16. Joehanns K, Bachvarova V, Vortkamp A. Reprint of: Heparan sulfate as a regulator of endochondral ossification and osteochondroma development. Matrix Biol. 2014; 35:239–247. [PubMed: 24726293]
17. Busse-Wicher M, Wicher KB, Kusche-Gullberg M. The extostosin family: proteins with many functions. Matrix Biol. 2014; 35:25–33. [PubMed: 24128412]
18. Schaefer L. Proteoglycans, key regulators of cell–matrix dynamics. Matrix Biol. 2014; 35:1–2. [PubMed: 24871042]
19. Douaiher J, Succar J, Lancerotto L, Gurish MF, Orgill DP, Hamilton MJ, et al. Development of mast cells and importance of their tryptase and chymase serine proteases in inflammation and wound healing. Adv Immunol. 2014; 122:211–252. [PubMed: 24507159]
20. Korpetinou A, Skandalis SS, Labropoulou VT, Smirlaki G, Noulas A, Karamanos NK, et al. Serglycin: at the crossroad of inflammation and malignancy. Front Oncol. 2014; 3:327. [PubMed: 24455486]
21. Kolset SO, Pejler G. Serglycin: a structural and functional chameleon with wide impact on immune cells. J Immunol. 2011; 187:4927–4933. [PubMed: 22049227]
22. Skliros A, Labropoulou VT, Papachristou DJ, Aletras A, Karamanos NK, Theocharis AD. Cell-surface serglycin promotes adhesion of myeloma cells to collagen type I and affects the expression of matrix metalloproteinases. FEBS J. 2013; 280:2342–2352. [PubMed: 23387827]
23. Purushothaman A, Toole BP. Serglycin proteoglycan is required for multiple myeloma cell adhesion, in vivo growth, and vascularization. J Biol Chem. 2014; 289:5499–5509. [PubMed: 24403068]
24. Vigetti D, Viola M, Karouss E, De LG, Passi A. Metabolic control of hyaluronan synthases. Matrix Biol. 2014; 35:8–13. [PubMed: 24134926]
25. Hascall VC, Wang A, Tammi M, Oikari S, Tammi R, Passi A, et al. The dynamic metabolism of hyaluronan regulates the cytosolic concentration of UDP-GlcNAc. Matrix Biol. 2014; 35:14–17. [PubMed: 24486448]
26. Reine TM, Vuong TT, Jenssen TG, Kolset SO. Serglycin secretion is part of the inflammatory response in activated primary human endothelial cells in vitro. Biochim Biophys Acta. 2014; 1840:2498–2505. [PubMed: 24513305]
27. Theocharis AD, Tzanakakis G, Karamanos NK. Proteoglycans in health and disease: novel proteoglycan roles in malignancy and their pharmacological targeting. FEBS J. 2010; 277:3904–3923. [PubMed: 20840587]
28. Korpetinou A, Skandalis SS, Moustakas A, Happonen KE, Tveit H, Prydz K, et al. Serglycin is implicated in the promotion of aggressive phenotype of breast cancer cells. PLoS One. 2013; 8:e78157. [PubMed: 24205138]
29. Bernfield M, Götte M, Park PW, Reizes O, Fitzgerald ML, Lincecum J, et al. Functions of cell surface heparan sulfate proteoglycans. Annu Rev Biochem. 1999; 68:729–777. [PubMed: 10872465]
30. Teng YH-F, Aquino RS, Park PW. Molecular functions of syndecan-1 in disease. Matrix Biol. 2012; 31:3–16. [PubMed: 22033227]
31. Leonova EI, Galzitskaya OV. Comparative characteristics of the structure and function for animal syndecan-1 proteins. Mol Biol. 2013; 47:446–452.
32. De RG, Evans AR, Kay E, Woodfin A, McKay TR, Nourshargh S, et al. Shed syndecan-2 inhibits angiogenesis. J Cell Sci. 2014; 127:4788–4799. [PubMed: 25179601]
33. Iozzo RV, San Antonio JD. Heparan sulfate proteoglycans: heavy hitters in the angiogenesis arena. J Clin Invest. 2001; 108:349–355. [PubMed: 11489925]
34. Choi Y, Chung H, Jung H, Couchman JR, Oh E-S. Syndecan as cell surface receptors: unique structure equates with functional diversity. Matrix Biol. 2011; 30:93–99. [PubMed: 21062643]
35. Christianson HC, Belting M. Heparan sulfate proteoglycan as a cell-surface endocytosis receptor. Matrix Biol. 2014; 35:51–55. [PubMed: 24145152]
36. Fuki IV, Kuhn KM, Lomazov IR, Rothman VL, Tuszyński GP, Iozzo RV, et al. The syndecan family of proteoglycans. Novel receptors mediating internalization of atherogenic lipoproteins in vitro. J Clin Invest. 1997; 100:1611–1622. [PubMed: 9294130]
37. Stanford KL, Bishop JR, Foley EM, Gonzales JC, Niesman IR, Witztum JL, et al. Syndecan-1 is the primary heparan sulfate proteoglycan mediating hepatic clearance of triglyceride-rich lipoproteins in mice. J Clin Invest. 2009; 119:3236–3245. [PubMed: 19805913]
38. Deng Y, Foley EM, Gonzales JC, Gordts PL, Li Y, Esko JD. Shedding of syndecan-1 from human hepatocytes alters very low density lipoprotein clearance. Hepatology. 2014; 55:277–286. [PubMed: 21898481]
39. Yang Y, Yaccoby S, Liu W, Langford JK, Pumphrey CY, Theus A, et al. Soluble syndecan-1 promotes growth of myeloma tumors in vivo. Blood. 2002; 100:610–617. [PubMed: 12091355]
40. Yang Y, MacLeod V, Miao H-Q, Theus A, Zhan F, Shaughnessy JD, et al. Heparanase enhances syndecan-1 shedding. A novel mechanism for stimulation of tumor growth and metastasis. J Biol Chem. 2007; 282:13326–13333. [PubMed: 17347152]
41. Sanderson RD, Yang Y. Syndecan-1: a dynamic regulator of the myeloma microenvironment. Clin Exp Metastasis. 2008; 25:149–159. [PubMed: 18027090]
42. Sanderson RD, Iozzo RV. Targeting heparanase for cancer therapy at the tumor–matrix interface. Matrix Biol. 2012; 31:283–284. [PubMed: 22655968]
43. Ramani VC, Sanderson RD. Chemotherapy stimulates syndecan-1 shedding: a potentially negative effect of treatment that may promote tumor relapse. Matrix Biol. 2014; 35:215–222. [PubMed: 24145151]
44. Purushothaman A, Uyama T, Kobayashi F, Yamada S, Sugahara K, Rapraeger AC, et al. Heparanase-enhanced shedding of syndecan-1 by myeloma cells promotes endothelial invasion and angiogenesis. Blood. 2010; 115:2449–2457. [PubMed: 20097882]
45. Zong F, Fthenou E, Wolmer N, Hollosi P, Kovalszky I, Szilak L, et al. Syndecan-1 and FGF-2, but not FGF receptor-1, share a common transport route and co-localize with heparanase in the nuclei of mesenchymal tumor cells. PLoS One. 2009; 4:e7346. [PubMed: 19802384]
46. Kovalszky I, Dudás J, Oláh-Nagy J, Pogány G, Töváry J, Timár J, et al. Inhibition of DNA topoisomerase I activity by heparan sulfate and regulation by basic fibroblast growth factor. Mol Cell Biochem. 1998; 183:11–23. [PubMed: 9655174]
47. Purushothaman A, Hurst DR, Pisano C, Mizumoto S, Sugahara K, Sanderson RD. Heparanase-mediated loss of nuclear syndecan-1 enhances histone acetyltransferase (HAT) activity to promote expression of genes that drive an aggressive tumor phenotype. J Biol Chem. 2011; 286:30377–30383. [PubMed: 21757697]
48. Stewart MD, Ramani VC, Sanderson RD. Shed syndecan-1 translocates to the nucleus of cells delivering growth factors and inhibiting histone acetylation: a novel mechanism of tumor–host crosstalk. J Biol Chem. 2015; 290:941–949. [PubMed: 25404732]
49. Nishiyama A, Dahlin KJ, Prince JT, Johnstone SR, Stallcup WB. The primary structure of NG2, a novel membrane-spanning proteoglycan. J Cell Biol. 1991; 114:359–371. [PubMed: 1906475]
50. Price MA, Wanshura LEC, Yang J, Carlson J, Xiang B, Li G, et al. CSPG4, a potential therapeutic target, facilitates malignant progression of melanoma. Pigment Cell Melanoma Res. 2011; 24:1148–1157. [PubMed: 22004131]

Matrix Biol. Author manuscript; available in PMC 2016 May 06.
55. You W-K, Yotsumoto F, Sakimura K, Adams RH, Stallcup WB. NG2 proteoglycan promotes tumor vascularization via integrin-dependent effects on pericyte function. Angiogenesis. 2014; 17:61–76. [PubMed: 23925489]

56. Cattaruzza S, Ozerdem U, Denzel M, Ranscht B, Bulian P, Cavallaro U, Zanocco D, Colombatti A, Stallcup WB, Perris R. Multivalent proteoglycan modulation of FGF mitogenic responses in perivascular cells. Angiogenesis. 2013; 16:309–327. [PubMed: 23124902]

57. Cattaruzza S, Nicolosi PA, Braghetta P, Pazzaglia L, Benassi MS, Picci P, et al. NG2/CSPG4-collagen type VI interplays putatively involved in the microenvironmental control of tumour engraftment and local expansion. J Mol Cell Biol. 2013; 5:176–193. [PubMed: 23559515]

58. Wang J, Svendsen A, Kmieciak J, Immervoll H, Skaftnesmo KO, Planagumà J, et al. Targeting the NG2/CSPG4 proteoglycan retards tumour growth and angiogenesis in preclinical models of GBM and melanoma. PLoS One. 2011; 6:e23062. [PubMed: 21829586]

59. Poli A, Wang J, Domingues O, Planagumà J, Yan T, Rygh CB, et al. Targeting glioblastoma with NK cells and mAb against NG2/CSPG4 prolongs animal survival. Oncotarget. 2013; 4:1527–1546. [PubMed: 24127551]

60. Biname F, Sakry D, Dimou L, Jolivel V, Trotter J. NG2 regulates directional migration of oligodendrocyte precursor cells via Rho GTPases and polarity complex proteins. J Neurosci. 2013; 33:10858–10874. [PubMed: 23804106]

61. Biname F. Transduction of extracellular cues into cell polarity: the role of the transmembrane proteoglycan NG2. Mol Neurobiol. 2014; 50:482–493. [PubMed: 24390567]

62. Estrada B, Gisselbrecht SS, Michelson AM. The transmembrane protein Perdido interacts with Grip and integrins to mediate myotube projection and attachment in the Drosophila embryo. Development. 2007; 134:4469–4478. [PubMed: 18039972]

63. Perez-Moreno JJ, Bischoff M, Martin-Bermudo MD, Estrada B. The conserved transmembrane proteoglycan Perdido/Kon-tiki is essential for myofibrillogenesis and sarcomeric structure in Drosophila. J Cell Sci. 2014; 127:3162–3173. [PubMed: 24794494]

64. Yuan P, Zhang H, Cui C, Zhu S, Zhou Y, Yang X, et al. Chondroitin sulfate proteoglycan 4 functions as the cellular receptor for Clostridium difficile toxin B. Cell Res. 2014; 25:157–168. [PubMed: 25547119]

65. López-Casillas F, Cheifetz S, Doody J, Andres JL, Lane WS, Massagué J. Structure and expression of the membrane proteoglycan betaglycan, a component of the TGF-β receptor system. Cell. 1991; 67:785–795. [PubMed: 1657406]

66. Wang Z-F, Lin HY, Ng-Eaton E, Downward J, Lodish HF, Weinberg RA. Expression cloning and characterization of the TFG-β type III receptor. Cell. 1991; 67:797–805. [PubMed: 1657407]

67. Lin SJ, Hu Y-X, Zhu J, Woodruff TK, Jardetzky TS. Structure of betaglycan zona pellucida (ZP)-C domain provides insights into ZP-mediated protein polymerization and TGF-β binding. Proc Natl Acad Sci U S A. 2011; 108:5232–5236. [PubMed: 21402931]

68. Diestel U, Resch M, Meinhardt K, Weiler S, Hellmann TV, Mueller TD, et al. Identification of a novel TGF-β-binding site in the zona pellucida C-terminal (ZP-C) domain of TGF-β-receptor-3 (TGFR-3). PLoS One. 2013; 8:e67214. [PubMed: 23826237]

69. Lewis KA, Gray PC, Blount AL, MacConell LA, Wiater E, Bilezilkjian LM, et al. Betaglycan binds inhibin and can mediate functional antagonism of activin signalling. Nature. 2000; 404:411–414. [PubMed: 10746731]

70. Kirkbride KC, Townsend TA, Bruinsma MW, Barnett JV, Blobe GC. Bone morphogenetic proteins signal through the transforming growth factor-β type III receptor. J Biol Chem. 2008; 283:7628–7637. [PubMed: 18184661]

71. Andres JL, Ronstrand L, Cheifetz S, Massagué J. Purification of the transforming growth factor-β (TGF-β) binding proteoglycan betaglycan. J Biol Chem. 1991; 266:23282–23287. [PubMed: 1744125]

72. Bilandzic M, Wang Y, Ahmed N, Luwor RB, Zhu HJ, Findlay JK, et al. Betaglycan blocks metastatic behaviors in human granulosa cell tumors by suppressing NFkappaB-mediated induction of MMP2. Cancer Lett. 2014; 354:107–114. [PubMed: 25128652]
73. Boivin WA, Shackleford M, Hoek AV, Zhao H, Hackett TL, Knight DA, et al. Granzyme B cleaves decorin, biglycan and soluble betaglycan, releasing active transforming growth factor-β1. PLoS One. 2012; 7:e33163. [PubMed: 22479366]

74. Elderbroom JL, Huang JJ, Gatza CE, Chen J, How T, Starr M, et al. Ectodomain shedding of TβRIII is required for TβRIII-mediated suppression of TGF-β signaling and breast cancer migration and invasion. Mol Biol Cell. 2014; 25:2320–2332. [PubMed: 24966170]

75. Bilandzic M, Stenvers KL. Betaglycan: a multifunctional accessory. Mol Cell Endocrinol. 2011; 339:180–189. [PubMed: 21550381]

76. Bernabeu C, Lopez-Novoa JM, Quintanilla M. The emerging role of TGF-β superfamily coreceptors in cancer. Biochim Biophys Acta. 2009; 1792:954–973. [PubMed: 19607914]

77. Maurel P, Rauch U, Flad D, Margolis RK, Margolis RU. Phosphacan, a chondroitin sulfate proteoglycan of brain that interacts with neurons and neural cell-adhesion molecules, is an extracellular variant of receptor-type protein tyrosine phosphatase. Proc Natl Acad Sci U S A. 1994; 91:2512–2516. [PubMed: 7511813]

78. Liu BP, Cafferty WBJ, Budel SO, Strittmatter SM. Extracellular regulators of axonal growth in the adult central nervous system. Philos Trans R Soc B. 2006; 361:1593–1610.

79. Zimmermann DR, Dours-Zimmermann MT. Extracellular matrix of the central nervous system: from neglect to challenge. Histochem Cell Biol. 2008; 130:635–653. [PubMed: 18696101]

80. Theocharidis U, Long K, Ffrench-Constant C, Faissner A. Regulation of the neural stem cell compartment by extracellular matrix constituents. Prog Brain Res. 2014; 214:3–28. [PubMed: 25410351]

81. Filmus J, Capurro M, Rast J. Glypicans. Genome Biol. 2008; 9:224. [PubMed: 18505598]

82. Capurro M, Xiang YY, Lobe C, Filmus J. Glypican-3 promotes the growth of hepatocellular carcinoma by stimulating canonical Wnt signaling. Cancer Res. 2005; 65:6245–6254. [PubMed: 16024626]

83. Capurro M, Xu P, Shi W, Li F, Jia A, Filmus J. Glypican-3 inhibits Hedgehog signaling during development by competing with Patched for Hedgehog binding. Dev Cell. 2008; 14:700–711. [PubMed: 18477453]

84. Filmus J, Capurro M. The role of glypicans in Hedgehog signaling. Matrix Biol. 2014; 35:248–252. [PubMed: 24412155]

85. Capurro M, Martin T, Shi W, Filmus J. Glypican-3 binds to Frizzled and plays a direct role in the stimulation of canonical Wnt signaling. J Cell Sci. 2014; 127:1565–1575. [PubMed: 24496449]

86. Svensson G, Linse S, Mani K. Chemical and thermal unfolding of glypican-1: protective effect of heparan sulfate against heat-induced irreversible aggregation. Biochemistry. 2009; 48:9994–10004. [PubMed: 19775117]

87. Kim MS, Saunders AM, Hamaoka BY, Beachy PA, Leahy DJ. Structure of the protein core of the glyptic Dally-like and localization of a region important for hedgehog signaling. Proc Natl Acad Sci U S A. 2011; 108:13112–13117. [PubMed: 21828006]

88. Svensson G, Awad W, Hakansson M, Mani K, Logan DT. Crystal structure of N-glycosylated human glypican-1 core protein: structure of two loops evolutionarily conserved in vertebrate glypican-1. J Biol Chem. 2012; 287:14040–14051. [PubMed: 22351761]

89. Capurro MI, Li F, Filmus J. Overgrowth of a mouse model of Simpson-Golabi-Behmel syndrome is partly mediated by Indian hedgehog. EMBO Rep. 2009; 10:901–907. [PubMed: 19590577]

90. Capurro M, Shi W, Izumikawa T, Filmus J. Processing by convertases is required for Glypican-3-induced inhibition of Hedgehog signaling. J Biol Chem. 2015 [in press].

91. Noonan DM, Fulle A, Valente P, Cai S, Horigan E, Sasaki M, et al. The complete sequence of perlecan, a basement membrane heparan sulfate proteoglycan, reveals extensive similarity with laminin A chain, low density lipoprotein-receptor, and the neural cell adhesion molecule. J Biol Chem. 1991; 266:22939–22947. [PubMed: 1744087]

92. Murdoch AD, Dodge GR, Cohen I, Tuan RS, Iozzo RV. Primary structure of the human heparan sulfate proteoglycan from basement membrane (HSPG2/perlecan). A chimeric molecule with multiple domains homologous to the low density lipoprotein receptor, laminin, neural cell adhesion molecules, and epidermal growth factor. J Biol Chem. 1992; 267:8544–8557. [PubMed: 1569102]
93. Cohen IR, Grässel S, Murdoch AD, Iozzo RV. Structural characterization of the complete human perlecan gene and its promoter. Proc Natl Acad Sci U S A. 1993; 90:10404–10408. [PubMed: 8234307]

94. Iozzo RV, Pillarsetti J, Sharma B, Murdoch AD, Danielson KG, Uitto J, et al. Structural and functional characterization of the human perlecan gene promoter. Transcriptional activation by transforming factor-β via a nuclear factor 1-binding element. J Biol Chem. 1997; 272:5219–5228. [PubMed: 9030592]

95. Sharma B, Iozzo RV. Transcriptional silencing of perlecan gene expression by interferon-γ. J Biol Chem. 1998; 273:4642–4646. [PubMed: 9468523]

96. Iozzo RV. Basement membrane proteoglycans: from cellar to ceiling. Nat Rev Mol Cell Biol. 2005; 6:646–656. [PubMed: 16064139]

97. Farach-Carson MC, Warren CR, Harrington DA, Carson DD. Border patrol: insights into the unique role of perlecan/heparan sulfate proteoglycan 2 at cell and tissue borders. Matrix Biol. 2014; 34:64–79. [PubMed: 24001398]

98. Carson DD, Tang J-P, Julian J. Heparan sulfate proteoglycan (perlecan) expression by mouse embryos during acquisition of attachment competence. Dev Biol. 1993; 155:97–106. [PubMed: 8416848]

99. Iozzo RV, Cohen IR, Grässel S, Murdoch AD. The biology of perlecan: the multifaceted heparan sulphate proteoglycan of basement membranes and pericellular matrices. Biochem J. 1994; 302:625–639. [PubMed: 7945186]

100. Farach-Carson MC, Carson DD. Perlecan — a multifunctional extracellular proteoglycan scaffold. Glycobiology. 2007; 17:897–905. [PubMed: 17442708]

101. Handler M, Yurchenco PD, Iozzo RV. Developmental expression of perlecan during murine embryogenesis. Dev Dyn. 1997; 210:130–145. [PubMed: 9337134]

102. Iozzo RV. Biosynthesis of heparan sulfate proteoglycan by human colon carcinoma cells and its localization at the cell surface. J Cell Biol. 1984; 99:403–417. [PubMed: 6235235]

103. Iozzo RV. Turnover of heparan sulfate proteoglycan in human colon carcinoma cells. A quantitative biochemical and autoradiographic study. J Biol Chem. 1987; 262:1888–1900. [PubMed: 2948961]

104. Iozzo RV. Perlecan: a gem of a proteoglycan. Matrix Biol. 1994; 14:203–208. [PubMed: 7921536]

105. Murdoch AD, Liu B, Schwarting R, Tuan RS, Iozzo RV. Widespread expression of perlecan proteoglycan in basement membranes and extracellular matrices of human tissues as detected by a novel monoclonal antibody against domain III and by in situ hybridization. J Histochem Cytochem. 1994; 42:239–249. [PubMed: 7507142]

106. Whitelock JM, Iozzo RV. Heparan sulfate: a complex polymer charged with biological activity. Chem Rev. 2005; 105:2745–2764. [PubMed: 16011323]

107. Whitelock JM, Melrose J, Iozzo RV. Diverse cell signaling events modulated by perlecan. Biochemistry. 2008; 47:11174–11183. [PubMed: 18826258]

108. Lord MS, Jung M, Cheng B, Whitelock JM. Transcriptional complexity of the HSPG2 gene in the human mast cell line, HMC-1. Matrix Biol. 2014; 35:123–131. [PubMed: 24365408]

109. Dodge GR, Kovalsky I, Hassell JR, Iozzo RV. Transforming growth factor β alters the expression of heparan sulfate proteoglycan in human colon carcinoma cells. J Biol Chem. 1990; 265:18023–18029. [PubMed: 1698783]

110. Whitelock JM, Murdoch AD, Iozzo RV, Underwood PA. The degradation of human endothelial cell-derived perlecan and release of bound basic fibroblast growth factor by stromelysin, collagenase, plasmin and heparanases. J Biol Chem. 1996; 271:10079–10086. [PubMed: 8626565]

111. Reiland J, Sanderson RD, Waguespack M, Barker SA, Long R, Carson DD, et al. Heparanase degrades syndecan-1 and perlecan heparan sulfate: functional implications for tumor cell invasion. J Biol Chem. 2004; 279:8047–8055. [PubMed: 14630925]

112. Grindel BJ, Martinez JR, Pennington CL, Muldoon M, Stave J, Chung LW, et al. Matrilysin/matrix metalloproteinase-7 (MMP7) cleavage of perlecan/HSPG2 creates a molecular switch to alter prostate cancer cell behavior. Matrix Biol. 2014; 36:64–76. [PubMed: 24833109]

Matrix Biol. Author manuscript; available in PMC 2016 May 06.
113. Iozzo, RV. Proteoglycans: structure, biology and molecular interactions. New York, New York: Marcel Dekker, Inc.; 2000.

114. Whitelock JM, Graham LD, Melrose J, Murdoch AD, Iozzo RV, Underwood PA. Human perlecan immunopurified from different endothelial cell sources has different adhesive properties for vascular cells. Matrix Biol. 1999; 18:163–178. [PubMed: 10372557]

115. Lord MS, Chuang CY, Melrose J, Davies MJ, Iozzo RV, Whitelock JM. The role of vascular-derived perlecan in modulating cell adhesion, proliferation and growth factor signaling. Matrix Biol. 2014; 35:112–122. [PubMed: 24509440]

116. Fuki I, Iozzo RV, Williams KJ. Perlecan heparan sulfate proteoglycan. A novel receptor that mediates a distinct pathway for ligand catabolism. J Biol Chem. 2000; 275:25742–25750. [PubMed: 10818109]

117. Nugent MA, Nugent HM, Iozzo RV, Sanchack K, Edelman ER. Perlecan is required to inhibit thrombosis after deep vascular injury and contributes to endothelial cell-mediated inhibition of intimal hyperplasia. Proc Natl Acad Sci U S A. 2000; 97:6722–6727. [PubMed: 10841569]

118. Laplante P, Raymond M-A, Labelle A, Abe J-I, Iozzo RV, Hebért M-J. Perlecan proteolysis induces α2β1 integrin and src-family kinases dependent anti-apoptotic pathway in fibroblasts in the absence of focal adhesion kinase activation. J Biol Chem. 2006; 281:30383–30392. [PubMed: 16882656]

119. Baker AB, Ettensohn DS, Jonas M, Nugent MA, Iozzo RV, Edelman ER. Endothelial cells provide feedback control for vascular remodeling through a mechanosensitive autocrine TGF-β signaling pathway. Circ Res. 2008; 103:289–297. [PubMed: 18583708]

120. Wilusz RE, DeFrate LE, Guilak F. A biomechanical role for perlecan in the pericellular matrix of articular cartilage. Matrix Biol. 2012; 31:320–327. [PubMed: 22659389]

121. Wilusz RE, Sanchez-Adams J, Guilak F. The structure and function of the pericellular matrix of articular cartilage. Matrix Biol. 2014; 39:25–32. [PubMed: 25172825]

122. Sher I, Zisman-Rozen S, Eliahu L, Whitelock JM, Maas-Szabowski N, Yamada Y, et al. Targeting perlecan in human keratinocytes reveals novel roles for perlecan in epidermal formation. J Biol Chem. 2006; 281:5178–5187. [PubMed: 16269412]

123. Ishijima M, Suzuki N, Hozumi K, Matsunobu T, Kosaki K, Kaneko H, et al. Perlecan modulates VEGF signaling and is essential for vascularization in endochondral bone formation. Matrix Biol. 2012; 31:234–245. [PubMed: 22421594]

124. Kaneko H, Ishijima M, Futami I, Tomikawa-Ichikawa N, Kosaki K, Sadatsuki R, et al. Synovial perlecan is required for osteophyte formation in knee osteoarthritis. Matrix Biol. 2013; 32:178–187. [PubMed: 23339836]

125. Mongiat M, Taylor K, Otto J, Aho S, Uitto J, Whitelock J, et al. The protein core of the proteoglycan perlecan binds specifically to fibroblast growth factor-7. J Biol Chem. 2000; 275:7095–7100. [PubMed: 10702276]

126. Mongiat M, Otto J, Oldershaw R, Ferrer F, Sato JD, Iozzo RV. Fibroblast growth factor-binding protein is a novel partner for perlecan protein core. J Biol Chem. 2001; 276:10263–10271. [PubMed: 11148217]

127. Mongiat M, Fu J, Oldershaw R, Greenhalgh R, Gown A, Iozzo RV. Perlecan protein core interacts with extracellular matrix protein 1 (ECM1), a glycoprotein involved in bone formation and angiogenesis. J Biol Chem. 2003; 278:17491–17499. [PubMed: 12604605]

128. Gonzalez EM, Mongiat M, Slater SJ, Baffa R, Iozzo RV. A novel interaction between perlecan protein core and progranulin: potential effects on tumor growth. J Biol Chem. 2003; 278:38113–38116. [PubMed: 12900424]

129. Li S, Scimon C, Norioka N, Nakano I, Okubo T, Yagi Y, et al. Activin A binds to perlecan through its pro-region that has heparin/heparan sulfate binding activity. J Biol Chem. 2011; 286:36645–36655. [PubMed: 20843788]

130. Cohen IR, Murdoch AD, Naso MF, Marchetti D, Berd D, Iozzo RV. Abnormal expression of perlecan proteoglycan in metastatic melanomas. Cancer Res. 1994; 54:5771–5774. [PubMed: 7954396]

131. Iozzo RV, Cohen I. Altered proteoglycan gene expression and the tumor stroma. Experientia. 1993; 49:447–455. [PubMed: 8500599]

Matrix Biol. Author manuscript; available in PMC 2016 May 06.
132. Mathiak M, Yenisey C, Grant DS, Sharma B, Iozzo RV. A role for perlecan in the suppression of growth and invasion in fibrosarcoma cells. Cancer Res. 1997; 57:2130–2136. [PubMed: 9187109]

133. Datta S, Pierce M, Datta MW. Perlecan signaling: helping hedgehog stimulate prostate cancer growth. Int J Biochem Cell Biol. 2006; 38:1855–1861. [PubMed: 16750652]

134. Kawahara R, Granato DC, Carnielli CM, Cervigne NK, Oliveria CE, Martinez CA, et al. Agrin and perlecan mediate tumorigenic processes in oral squamous cell carcinoma. PLoS One. 2014; 9:e115004. [PubMed: 25506919]

135. Lindner JR, Hillman PR, Barrett AL, Jackson MC, Perry TL, Park Y, et al. The Drosophila Perlecan gene trol regulates multiple signaling pathways in different developmental contexts. BMC Dev Biol. 2007; 7:121. [PubMed: 17980035]

136. Park Y, Rangel C, Reynolds MM, Caldwell MC, Johns M, Nayak M, et al. Drosophila perlecan modulates FGF and Hedgehog signals to activate neural stem cell division. Dev Biol. 2003; 253:247–257. [PubMed: 12645928]

137. Grigorian M, Liu T, Banerjee U, Hartenstein V. The proteoglycan Trol controls the architecture of the extracellular matrix and balances proliferation and differentiation of blood progenitors in the Drosophila lymph gland. Dev Biol. 2013; 384:301–312. [PubMed: 23510717]

138. Girós A, Morante J, Gil-Sanz C, Fairén A, Costell M. Perlecan controls neurogenesis in the developing telencephalon. BMC Dev Biol. 2007; 7:29. [PubMed: 17411441]

139. Xu Y, Ashline D, Liu L, Tassa C, Shaw SY, Ravid K, et al. The glycosylation-dependent interaction of perlecan core protein with LDL: implications for atherosclerosis. J Lipid Res. 2015; 56:266–276. [PubMed: 25528754]

140. Iozzo RV, Zoeller JJ, Nyström A. Basement membrane proteoglycans: modulators par excellence of cancer growth and angiogenesis. Mol Cells. 2009; 27:503–513. [PubMed: 19466598]

141. Iozzo RV, Sanderson RD. Proteoglycans in cancer biology, tumour microenvironment and angiogenesis. J Cell Mol Med. 2011; 15:1013–1031. [PubMed: 21155971]

142. Nugent MA, Iozzo RV. Fibroblast growth factor-2. Int J Biochem Cell Biol. 2000; 32:115–120. [PubMed: 10687947]

143. Ghiselli G, Eichstetter I, Iozzo RV. A role for the perlecan protein core in the activation of the keratinocyte growth factor receptor. Biochem J. 2001; 359:153–163. [PubMed: 11563979]

144. Smith SML, West LA, Hassell JR. The core protein of growth plate perlecan binds FGF-18 and alters its mitogenic effect on chondrocytes. Arch Biochem Biophys. 2007; 468:244–251. [PubMed: 17971291]

145. Murakami M, Simons M. Fibroblast growth factor regulation of neovascularization. Curr Opin Hematol. 2008; 15:215–220. [PubMed: 18391788]

146. Aviezzer D, Hecht D, Safran M, Eisinger M, David G, Yayon A. Perlecan, basal lamina proteoglycan, promotes basic fibroblast growth factor receptor binding, mitogenesis, and angiogenesis. Cell. 1994; 79:1005–1013. [PubMed: 7528102]

147. Sharma B, Handler M, Eichstetter I, Whitelock J, Nugent MA, Iozzo RV. Antisense targeting of perlecan blocks tumor growth and angiogenesis in vivo. J Clin Invest. 1998; 102:1599–1608. [PubMed: 9788974]

148. Aviezzer D, Iozzo RV, Noonan DM, Yayon A. Suppression of autocrine and paracrine functions of basic fibroblast growth factor by stable expression of perlecan antisense cDNA. Mol Cell Biol. 1997; 17:1938–1946. [PubMed: 9124141]

149. Zoeller JJ, Whitelock J, Iozzo RV. Perlecan regulates developmental angiogenesis by modulating the VEGF–VEGFR2 axis. Matrix Biol. 2009; 28:284–291. [PubMed: 19422911]

150. Vincent TL, McLean CJ, Full LE, Peston D, Saklatvala J. FGF-2 is bound to perlecan in the pericellular matrix of articular cartilage, where it acts as a chondrocyte mechanotransducer. Osteoarthritis Cartilage. 2007; 15:752–763. [PubMed: 17368052]

151. Chuang CY, Lord MS, Melrose J, Rees MD, Knox SM, Freeman C, et al. Heparan sulfate-dependent signaling of fibroblast growth factor 18 by chondrocyte-derived perlecan. Biochemistry. 2010; 49:5524–5532. [PubMed: 20507176]
152. Muthusamy A, Cooper CR, Gomes RR Jr. Soluble perlecan domain I enhances vascular endothelial growth factor-165 activity and receptor phosphorylation in human bone marrow endothelial cells. BMC Biochem. 2010; 11:43. [PubMed: 21047416]

153. Patel VN, Knox SM, Likar KM, Lathrop CA, Hossain R, Eftekhar S, et al. Heparanase cleavage of perlecan heparan sulfate modulates FGF10 activity during ex vivo submandibular gland branching morphogenesis. Development. 2007; 134:4177–4186. [PubMed: 17959718]

154. Costell M, Carmona R, Gustafsson E, González-Iriarte M, Fässler R, Munoz-Chápuli R. Hyperplastic conotruncal endocardial cushions and transposition of great arteries in perlecan-null mice. Circ Res. 2002; 91:158–164. [PubMed: 12142349]

155. Zoeller JJ, McQuillan A, Whitelock J, Ho S-Y, Iozzo RV. A central function for perlecan in skeletal muscle and cardiovascular development. J Cell Biol. 2008; 181:381–394. [PubMed: 18426981]

156. González-Iriarte M, Carmona R, Pérez-Pomares JM, Macías D, Costell M, Munoz-Chápuli R. Development of the coronary arteries in a murine model of transposition of great arteries. J Mol Cell Cardiol. 2003; 35:795–802. [PubMed: 12818570]

157. Gustafsson E, Almonte-Becerril M, Bloch W, Costell M. Perlecan maintains microvessel integrity in vivo and modulates their formation in vitro. PLoS One. 2013; 8:e53715. [PubMed: 23320101]

158. Rossi M, Morita H, Sormunen R, Airenne S, Kreivi M, Wang L, et al. Heparan sulfate chains of perlecan are indispensable in the lens capsule but not in the kidney. EMBO J. 2003; 22:236–245. [PubMed: 12514129]

159. Zhou Z, Wang J, Cao R, Morita H, Soininen R, Chan KM, et al. Impaired angiogenesis, delayed wound healing and retarded tumor growth in perlecan heparan sulfate-deficient mice. Cancer Res. 2004; 64:4699–4702. [PubMed: 15256433]

160. Tran P-K, Tran-Lundmark K, Soininen R, Tryggvason K, Thyberg J, Hedin U. Increased intimal hyperplasia and smooth muscle cell proliferation in transgenic mice with heparan sulfate-deficient perlecan. Circ Res. 2004; 94:550–558. [PubMed: 14739157]

161. Gotha L, Lim SY, Osherov AB, Wolff R, Qiang B, Eshel I, et al. Heparan sulfate side chains have a critical role in the inhibitory effects of perlecan on vascular smooth muscle cell response to arterial injury. Am J Physiol Heart Circ Physiol. 2014; 307:H337–H345. [PubMed: 24858854]

162. Qiang B, Lim SY, Lekas M, Kuliszewski MA, Wolff R, Osherov AB, et al. Perlecan heparan sulfate proteoglycan is a critical determinant of angiogenesis in response to mouse hind-limb ischemia. Can J Cardiol. 2014; 30:1444–1451. [PubMed: 25249499]

163. Nonaka R, Iesaki T, de Vega S, Daida H, Okada T, Sasaki T, et al. Perlecan deficiency causes endothelial dysfunction by reducing the expression of endothelial nitric oxide synthase. Physiol Rep. 2015; 3 [in press].

164. Colombelli C, Palmisano M, Eshed-Eisenbach Y, Zambroni D, Pavoni E, Ferri C, et al. Perlecan is recruited by dystroglycan to nodes of Ranvier and binds the clustering molecule gliomedin. J Cell Biol. 2015; 208:313–329. [PubMed: 25646087]

165. Mongiat M, Sweeney S, San Antonio JD, Fu J, Iozzo RV. Endorepellin, a novel inhibitor of angiogenesis derived from the C terminus of perlecan. J Biol Chem. 2003; 278:4238–4249. [PubMed: 12435733]

166. Bix G, Fu J, Gonzalez E, Macro L, Barker A, Campbell S, et al. Endorepellin causes endothelial cell disassembly of actin cytoskeleton and focal adhesions through the α2β1 integrin. J Cell Biol. 2004; 166:97–109. [PubMed: 15240572]

167. Bix G, Castello R, Burrows M, Zoeller JJ, Weech M, Iozzo RA, et al. Endorepellin in vivo: targeting the tumor vasculature and retarding cancer growth and metabolism. J Natl Cancer Inst. 2006; 98:1634–1646. [PubMed: 17105986]

168. Woodall BP, Nystöm A, Iozzo RA, Eble JA, Niland S, Krieg T, et al. Integrin α2β1 is the required receptor for endorepellin angiostatic activity. J Biol Chem. 2008; 283:2335–2343. [PubMed: 18024432]

169. Willis, CD.; Schaefer, L.; Iozzo, RV. The biology of perlecan and its bioactive modules. In: Karamanos, NK., editor. Extracellular matrix: pathobiology and signaling. Berlin: Walter de Gruyter GmbH & Co. KG; 2012. p. 171-184.
170. Adkins JN, Varnum SM, Auberry KJ, Moore RJ, Angell NH, Smith RD, et al. Toward a human blood serum proteome: analysis by multidimensional separation coupled with mass spectrometry. Mol Cell Proteomics. 2002; 1:947–955. [PubMed: 12543931]

171. West L, Govindraj P, Koob TJ, Hassell JR. Changes in perlecan during chondrocyte differentiation in the fetal bovine rib growth plate. J Orthop Res. 2006; 24:1317–1326. [PubMed: 16705694]

172. Májek P, Reicheltová Z, Suttar J, Cermák J, Dyr JE. Plasma proteome changes associated with refractory cytopenia with multilineage dysplasia. Proteome Sci. 2011; 9:64. [PubMed: 21975265]

173. Oda O, Shinzato T, Ohbayashi K, Taike I, Kunimatsu M, Maeda K, et al. Purification and characterization of perlecan fragment in urine of end-stage renal failure patients. Clin Chim Acta. 1996; 255:119–132. [PubMed: 8937755]

174. González EM, Reed CC, Bix G, Fu J, Zhang Y, Gopalakrishnan B, et al. BMP-1/Tolloid-like metalloproteases process endorepellin, the angiostatic C-terminal fragment of perlecan. J Biol Chem. 2005; 280:7080–7087. [PubMed: 15591058]

175. O’Riordan E, Orlova TN, Patschan D, Kemp R, Chander PN, et al. Urinary proteomic analysis of chronic renal allograft nephropathy. Proteomics Clin Appl. 2008; 2:1025–1035. [PubMed: 21136903]

176. Soulez M, Pilon E-A, Dieudé M, Cardinal H, Brassard N, Qi S, et al. The perlecan fragment LG3 is a novel regulator of obliterator remodeling associated with allograft vascular rejection. Circ Res. 2012; 110:94–104. [PubMed: 22076637]

177. Gianazza E, Wait R, Begum S, Eberini I, Campagnoli M, Labo S, et al. Mapping the 5–50-kDa fraction of human amniotic fluid proteins by 2-DE and ESI-MS. Proteomics Clin Appl. 2007; 1:167–175. [PubMed: 21136666]

178. Vuadens F, Benay C, Crettaz D, Gallot D, Sapin V, Schneider P, et al. Identification of biologic markers of the premature rupture of fetal membranes: proteomic approach. Proteomics. 2003; 3:1521–1525. [PubMed: 12923777]

179. Thadikkaran L, Crettaz D, Siegenthaler MA, Gallot D, Sapin V, Iozzo RV, et al. The role of proteomics in the assessment of premature rupture of fetal membranes. Clin Chim Acta. 2005; 360:27–36. [PubMed: 15970282]

180. Tsangaris GT, Karamessinis P, Kolialexi A, Garbis SD, Antsaklis A, Mavrou A, et al. Proteomic analysis of amniotic fluid in pregnancies with Down syndrome. Proteomics. 2006; 6:4410–4419. [PubMed: 16847874]

181. Krishna J, Shah ZA, Merchant M, Klein JB, Gozal D. Urinary protein expression patterns in children with sleep-disordered breathing: preliminary findings. Sleep Med. 2006; 7:221–227. [PubMed: 16564219]

182. Raymond M-A, Désormeaux A, Laplante P, Vigneault N, Filep JG, Landry K, et al. Apoptosis of endothelial cells triggers a caspase-dependent anti-apoptotic paracrine loop active on vascular smooth muscle cells. FASEB J. 2004; 18:705–707. [PubMed: 14977881]

183. Mauri P, Scarpa A, Nascimbeni AC, Benazzi L, Parmagnani E, Mafficini A, et al. Identification of proteins released by pancreatic cancer cells by multidimensional protein identification technology: a strategy for identification of novel cancer markers. FASEB J. 2005; 19:1125–1127. [PubMed: 15985535]

184. Sweeney MC, Wavreille A-S, Park J, Butchar JP, Trindalapani S, Pei D. Decoding protein–protein interactions through combinatorial chemistry: sequence specificity of SHP-1, SHP-2, and SHIP SH2 domains. Biochemistry. 2005; 44:14932–14947. [PubMed: 16274240]

185. Grønborg M, Kristiansen T, Iwahori A, Chang R, Reddy R, Sato N, et al. Biomarker discovery from pancreatic cancer secretome using a differential proteomic approach. Mol Cell Proteomics. 2006; 5:157–171. [PubMed: 16215274]

Matrix Biol. Author manuscript; available in PMC 2016 May 06.
188. Aspinall-O'Dea M, Costello E. The pancreatic cancer proteome—recent advances and future promise. Proteomics Clin Appl. 2007; 1:1066–1079. [PubMed: 21136758]

189. Lee B, Clarke D, Al Ahmad A, Kahle M, Parham C, Auckland L, et al. Perlecan domain V is neuroprotective and proangiogenic following ischemic stroke in rodents. J Clin Invest. 2011; 121:3005–3023. [PubMed: 21747167]

190. Saini MG, Bix GJ. Oxygen-glucose deprivation (OGD) and interleukin-1 (IL-1) differentially modulate cathepsin B/L mediated generation of neuroprotective perlecan LG3 by neurons. Brain Res. 2012; 1438:65–74. [PubMed: 22244880]

191. Saini MG, Pinteaux E, Lee B, Bix GJ. Oxygen-glucose deprivation and interleukin-1α trigger the release of perlecan LG3 by cells of neurovascular unit. J Neurochem. 2011; 119:760–771. [PubMed: 21919908]

192. Chang JW, Kang U-B, Kim DH, Yi JK, Lee JW, Noh D-Y, et al. Identification of circulating endorepellin LG3 fragment: potential use as a serological biomarker for breast cancer. Proteomics Clin Appl. 2008; 2:23–32. [PubMed: 21136776]

193. Jung M, Lord MS, Cheng B, Lyons JG, Alkhouri H, Hughes JM, et al. Mast cells produce novel shorter forms of perlecan that contain functional endorepellin: a role in angiogenesis and wound healing. J Biol Chem. 2013; 288:3289–3304. [PubMed: 23235151]

194. San Antonio JD, Zoeller JJ, Habursky K, Turner K, Pimtong W, Burrows M, et al. A key role for the integrin α2β1 in experimental and developmental angiogenesis. Am J Pathol. 2009; 175:1338–1347. [PubMed: 19700757]

195. Nyström A, Shaik ZP, Gullberg D, Krieg T, Eckes B, Zent R, et al. Role of tyrosine phosphatase SHP-1 in the mechanism of endorepellin angiostatic activity. Blood. 2009; 114:4897–4906. [PubMed: 19789387]

196. Zoeller JJ, Iozzo RV. Proteomic profiling of endorepellin angiostatic activity on human endothelial cells. Proteome Sci. 2008; 6:7. [PubMed: 18269764]

197. Goyal A, Pal N, Concannon M, Paulk M, Doran M, Poluzzi C, et al. Endorepellin, the angiostatic module of perlecan, interacts with both the α2β1 integrin and vascular endothelial growth factor receptor 2 (VEGFR2). J Biol Chem. 2011; 286:25947–25962. [PubMed: 21596751]

198. Willis CD, Poluzzi C, Mongiat M, Iozzo RV. Endorepellin laminin-like globular repeat 1/2 domains bind Ig3–5 of vascular endothelial growth factor(VEGF) receptor 2 and block pro-angiogenic signaling by VEGFA in endothelial cells. FEBS J. 2013; 280:2271–2294. [PubMed: 23374253]

199. Bix G, Iozzo RV. Matrix revolutions: “tails” of basement-membrane components with angiostatic functions. Trends Cell Biol. 2005; 15:52–60. [PubMed: 15653078]

200. Goyal A, Poluzzi C, Willis AC, Smythies J, Shellard A, Neill T, et al. Endorepellin affects angiogenesis by antagonizing diverse VEGFR2- evoked signaling pathways: transcriptional repression of HIF-1α and VEGFA and concurrent inhibition of NFAT1 activation. J Biol Chem. 2012; 287:43543–43556. [PubMed: 23060442]

201. Poluzzi C, Casulli J, Goyal A, Mercer TJ, Neill T, Iozzo RV. Endorepellin evokes autophagy in endothelial cells. J Biol Chem. 2014; 289:16114–16128. [PubMed: 24737315]

202. Nitkin RM, Smith MA, Magill C, Fallon JR, Yao Y-MM, Wallace BG, et al. Identification of agrin, a synaptic organizing protein from Torpedo electric organ. J Cell Biol. 1987; 105:2471–2478. [PubMed: 2826489]

203. Tsen G, Hafteker W, Kröger S, Cole GJ. Agrin is a heparan sulfate proteoglycan. J Biol Chem. 1995; 270:3392–3399. [PubMed: 7852425]

204. Bezakova G, Rüegg MA. New insights into the roles of agrin. Nat Rev Mol Cell Biol. 2003; 4:295–308. [PubMed: 12671652]

205. Porten E, Seliger B, Schneider VA, Wöl S, Stangel D, Ramseger R, et al. The process-inducing activity of transmembrane agrin requires follistatin-like domains. J Biol Chem. 2010; 285:3114–3125. [PubMed: 19940118]

206. Denzer AJ, Sculthess T, Fauser C, Schumacher B, Kammerer RA, Engel J, et al. Electron microscopic structure of agrin and mapping of its binding site in laminin-1. EMBO J. 1998; 17:335–343. [PubMed: 9430625]
207. Winzen U, Cole GJ, Halfter W. Agrin is a chimeric proteoglycan with the attachment sites for heparan sulfate/chondroitin sulfate located in two multiple serine–glycine clusters. J Biol Chem. 2003; 278:30106–30114. [PubMed: 12773545]

208. Baerwald-De La Torre K, Winzen U, Halfter W, Bixby JL. Glycosaminoglycan-dependent and -independent inhibition of neurite outgrowth by agrin. J Neurochem. 2004; 90:50–61. [PubMed: 15198666]

209. Burgess RW, Dickman DK, Nunez L, Glass DJ, Sanes JR. Mapping sites responsible for interactions of agrin with neurons. J Neurochem. 2002; 83:271–284. [PubMed: 12423238]

210. Kim N, Stieglert AL, Cameron TO, Hallock PT, Gomez AM, Huang JH, et al. Lrp4 is a receptor for agrin and forms a complex with MuSK. Cell. 2008; 135:334–342. [PubMed: 18848351]

211. Stetefeld J, Alexandrescu AT, Maciejewski MW, Jenny M, Rathgeb-Szabo K, Schulthess T, et al. Modulation of agrin function by alternative splicing and Ca2+ binding. Structure. 2004; 12:503–515. [PubMed: 15016366]

212. Patel TR, Butler G, McFarlane A, Xie I, Overall CM, Stetefeld J. Site specific cleavage mediated by MMPs regulates function of agrin. PLoS One. 2012; 7:e43669. [PubMed: 22984437]

213. Smirnov SP, Barzaghi P, McKee KK, Ruegg MA, Yurchenco PD. Conjugation of LG domains of agrins and perlecan to polymerizing laminin-2 promotes acetylcholine receptor clustering. J Biol Chem. 2005; 280:41449–41457. [PubMed: 16219760]

214. Huze C, Bauche S, Richard P, Chevessier F, Guillet E, Gaudon K, et al. Identification of an agrin mutation that causes congenital myasthenia and affects synapse function. Am J Hum Genet. 2009; 85:155–167. [PubMed: 19631309]

215. Nicole S, Chaouch A, Torbergsen T, Bauche S, de BE, Fontenille MJ, et al. Agrin mutations lead to a congenital myasthenic syndrome with distal muscle weakness and atrophy. Brain. 2014; 137:2429–2443. [PubMed: 24951643]

216. Marneros AG, Olsen BR. Physiological role of collagen XVIII and endostatin. FASEB J. 2005; 19:716–728. [PubMed: 15857886]

217. Oh SP, Kamagata Y, Muragaki Y, Timmons S, Ooshima A, Olsen BR. Isolation and sequencing of cDNAs for proteins with multiple domains of Gly-Xaa-Yaa repeats identify a distinct family of collagenous proteins. Proc Natl Acad Sci U S A. 1994; 91:4229–4233. [PubMed: 8183893]

218. Rehn M, Pihlajaniemi T. α1(XVIII), a collagen chain with frequent interruptions in the collagenous sequence, a distinct tissue distribution, and homology with type XV collagen. Proc Natl Acad Sci U S A. 1994; 91:4234–4238. [PubMed: 8183894]

219. Muragaki Y, Timmons S, Griffith CM, Oh SP, Fadel B, Quertermous T, et al. Mouse Col18a1 is expressed in a tissue-specific manner as three alternative variants and is localized in basement membrane zones. Proc Natl Acad Sci U S A. 1995; 92:8763–8767. [PubMed: 7568013]

220. Rehn M, Hintikka E, Pihlajaniemi T. Primary structure of the alpha 1 chain of mouse type XVIII collagen, partial structure of the corresponding gene, and comparison of the alpha 1(XVIII) chain with its homologue, the alpha 1(XV) collagen chain. J Biol Chem. 1994; 269:13929–13935. [PubMed: 8188673]

221. Seppinen L, Pihlajaniemi T. The multiple functions of collagen XVIII in development and disease. Matrix Biol. 2011; 30:83–92.

222. Halfter W, Dong S, Schurer B, Cole GJ. Collagen XVIII is a basement membrane heparan sulfate proteoglycan. J Biol Chem. 1998; 273:25404–25412. [PubMed: 9738008]

223. Dong S, Cole GJ, Halfter W. Expression of collagen XVIII and localization of its glycosaminoglycan attachment sites. J Biol Chem. 2003; 278:1700–1707. [PubMed: 12433925]

224. Rehn M, Veikkola T, Kuuk-Valdre E, Nakamura H, Ilmonen M, Lombardo CR, et al. Interaction of endostatin with integrins implicated in angiogenesis. Proc Natl Acad Sci U S A. 2001; 98:1024–1029. [PubMed: 11158588]

225. Sudhakar A, Sugimoto H, Yang C, Lively J, Zeisberg M, Kalluri R. Human tumstatin and human endostatin exhibit distinct antiangiogenic activities mediated by αvβ3 and α5β1 integrins. Proc Natl Acad Sci U S A. 2003; 100:4766–4771. [PubMed: 12682293]

226. Kim Y-M, Hwang S, Kim Y-M, Pyun B-J, Kim T-Y, Lee S-T, et al. Endostatin blocks vascular endothelial growth factor-mediated signaling via direct interaction with KDR/Flik-1. J Biol Chem. 2002; 277:27872–27879. [PubMed: 12029087]
227. Nguyen TMB, Subramanian IV, Xiao X, Ghosh G, Nguyen P, Kelekar A, et al. Endostatin induces autophagy in endothelial cells by modulating Beclin 1 and β-catenin levels. J Cell Mol Med. 2009; 13:3687–3698. [PubMed: 19298526]

228. Abdollahi A, Hahnfeldt P, Maercker C, Gröne H-J, Debus J, Ansorge W, et al. Endostatin’s antiangiogenic signaling network. Mol Cell. 2004; 13:649–663. [PubMed: 15023336]

229. Murphy-Ullrich JE, Iozzo RV. Thrombospondins in physiology and disease: new tricks for old dogs. Matrix Biol. 2012; 31:152–154. [PubMed: 22265891]

230. Sweetwyne MT, Murphy-Ullrich JE. Thrombospondin 1 in tissue repair and fibrosis: TGF-β-dependent and independent mechanisms. Matrix Biol. 2012; 31:178–186. [PubMed: 22266026]

231. Fukai N, Eklund L, Marneros AG, Oh SP, Keene DR, Tamarkin L, et al. Lack of collagen XVIII/endostatin results in eye abnormalities. EMBO J. 2002; 21:1535–1544. [PubMed: 11927538]

232. Ylikärppä R, Eklund L, Sormunen R, Kontiola AI, Utriainen A, Määtä M, et al. Lack of type XVIII collagen results in anterior ocular defects. FASEB J. 2003; 17:2257–2259. [PubMed: 14525950]

233. Sertie AL, Sossi V, Camargo AA, Zatz M, Brahe C, Passos-Bueno MR. Collagen XVIII, containing an endogenous inhibitor of angiogenesis and tumor growth, plays a critical role in the maintenance of retinal structure and in neural tube closure (Knobloch syndrome). Hum Mol Genet. 2000; 9:2051–2058. [PubMed: 10942434]

234. Suzuki OT, Sertie AL, Der KV, Kok F, Carpenter M, Murray J, et al. Molecular analysis of collagen XVIII reveals novel mutations, presence of a third isoform, and possible genetic heterogeneity in Knobloch syndrome. Am J Hum Genet. 2002; 71:1320–1329. [PubMed: 12415512]

235. Moulton KS, Olsen BR, Sonn S, Fukai N, Zurakowski D, Zeng X. Loss of collagen XVIII enhances neovascularization and vascular permeability in atherosclerosis. Circulation. 2004; 110:1330–1336. [PubMed: 15313955]

236. Bishop JR, Passos-Bueno MR, Fong L, Stanford KI, Gonzales JC, Yeh E, et al. Deletion of basement membrane heparan sulfate proteoglycan type XVIII collagen causes hypertriglyceridemia in mice and humans. PLoS One. 2011; 5:e13919. [PubMed: 21085708]

237. Seppinen L, Sormunen R, Soini Y, Elamaa H, Heljasvaara R, Pihlajaniemi T. Lack of collagen XVIII accelerates cutaneous wound healing, while overexpression of its endostatin domain leads to delayed healing. Matrix Biol. 2008; 27:535–546. [PubMed: 18455382]

238. Eklund L, Piuhola J, Komulainen J, Rmumen R, Gvarrasopone C, Sisler R, et al. Lack of type XVII collagen causes a skeletal myopathy and cardiovascular defects in mice. Proc Natl Acad Sci U S A. 2001; 98:1194–1199. [PubMed: 11158616]

239. Zaferani A, Talsma DT, Yazdani S, Celie JW, Aikio M, Heljasvaara R, et al. Basement membrane zone collagens XV and XVIII/proteoglycans mediate leukocyte influx in renal ischemia/reperfusion. PLoS One. 2014; 9:e106732. [PubMed: 25188299]

240. Aikio M, Elamaa H, Vicente D, Izzii V, Kaur I, Seppinen L, et al. Specific collagen XVIII isoforms promote adipose tissue accrual via mechanisms determining adipocyte number and affect fat deposition. Proc Natl Acad Sci U S A. 2014; 111:E3043–E3052. [PubMed: 25024173]

241. Wight, TN.; Toole, BP.; Hascall, VC. Hyaluronan and the aggregating proteoglycans. In: Mecham, RP., editor. The extracellular matrix: an overview. Berlin: Springer-Verlag; 2011. p. 147-195.

242. Heinegård D. Proteoglycans and more—from molecules to biology. Int J Exp Pathol. 2009; 90:575–586. [PubMed: 19958398]

243. Kiani C, Chen L, Wu YJ, Yee AJ, Yang BB. Structure and function of aggrecan. Cell Res. 2002; 12:19–32. [PubMed: 11942407]

244. Morawski M, Brückner G, Arendt T, Matthews RT. Aggrecan: beyond the cartilage and into the brain. Int J Biochem Cell Biol. 2012; 44:690–693. [PubMed: 22297263]

245. Aspberg A, Miura R, Bourdoulous S, Shimonaka M, Heinegård D, Schachner M, et al. The c-type lectin domains of lecticans, a family of aggregating chondroitin sulfate proteoglycans, bind tenascin-R by protein–protein interactions independent of carbohydrate moiety. Proc Natl Acad Sci U S A. 1998; 94:10116–10121. [PubMed: 9294172]
246. Reginato AM, Iozzo RV, Jimenez SA. Formation of nodular structures resembling mature articular cartilage in long-term primary cultures of human fetal epiphyseal chondrocytes on a hydrogel substrate. Arthritis Rheum. 1994; 37:1338–1349. [PubMed: 7945499]

247. Vertel BM. The ins and outs of aggrecan. Trends Cell Biol. 1995; 5:458–464. [PubMed: 14732030]

248. Decker RS, Koyama E, Pacifici M. Genesis and morphogenesis of limb synovial joints and articular cartilage. Matrix Biol. 2014; 39:5–10. [PubMed: 25172830]

249. Hsueh MF, Onnerfjord P, Kraus VB. Biomarkers and proteomic analysis of osteoarthritis. Matrix Biol. 2014; 39:56–66. [PubMed: 25179675]

250. Zimmermann DR, Ruoslahti E. Multiple domains of the large fibroblast proteoglycan, versican. EMBO J. 1989; 8:2975–2981. [PubMed: 2583089]

251. Shinomura T, Nishida Y, Ito K, Kimata K. cDNA cloning of PG-M, a large chondroitin sulfate proteoglycan expressed during chondrogenesis in chick limb buds. Alternative spliced multiforms of PG-M and their relationships to versican. J Biol Chem. 1993; 268:14461–14469. [PubMed: 8314802]

252. Shinomura T, Zako M, Ito K, Ujita M, Kimata K. The gene structure and organization of mouse PG-M, a large chondroitin sulfate proteoglycan. J Biol Chem. 1995; 270:10328–10333. [PubMed: 7730339]

253. Iozzo RV, Naso MF, Cannizzaro LA, Wasmuth JJ, McPherson JD. Mapping of the versican proteoglycan gene (CSPG2) to the long arm of human chromosome 5 (5q12–5q14). Genomics. 1992; 14:845–851. [PubMed: 14786644]

254. Naso MF, Morgan JL, Burchberg AM, Siracusa LD, Iozzo RV. Expression pattern and mapping of the murine versican gene (Cspg2) to chromosome 13. Genomics. 1995; 29:297–300. [PubMed: 8530092]

255. Naso MF, Zimmermann DR, Iozzo RV. Characterization of the complete genomic structure of the human versican gene and functional analysis of its promoter. J Biol Chem. 1994; 269:32999–33008. [PubMed: 7528742]

256. LeBaron RG, Zimmermann DR, Ruoslahti E. Hyaluronate binding properties of versican. J Biol Chem. 1992; 267:10003–10010. [PubMed: 1577773]

257. Kang I, Yoon DW, Braun KR, Wight TN. Expression of versican V3 by arterial smooth muscle cells alters tumor growth factor beta (TGFbeta)-, epidermal growth factor (EGF)-, and nuclear factor kappaB (NFkappaB)-dependent signaling pathways, creating a microenvironment that resists monocyte adhesion. J Biol Chem. 2014; 289:15393–15404. [PubMed: 24719328]

258. Kischel P, Waltregny D, Dumont B, Turtori A, Greffe Y, Kirsch S, et al. Versican overexpression in human breast cancer lesions: known and new isoforms for stromal tumor targeting. Int J Cancer. 2010; 126:640–650. [PubMed: 19662555]

259. Zako M, Shinomura T, Kimata K. Alternative splicing of the unique “PLUS” domain of chicken PG-M/versican is developmentally regulated. J Biol Chem. 1997; 272:9325–9331. [PubMed: 9083069]

260. Wight TN, Kinsella MG, Evanko SP, Potter-Perigo S, Merrilees MJ. Versican and the regulation of cell phenotype in disease. Biochim Biophys Acta. 2014; 1840:2441–2451. [PubMed: 24401530]

261. Wight TN, Kang I, Merrilees MJ. Versican and the control of inflammation. Matrix Biol. 2014; 35:152–161. [PubMed: 24513039]

262. Chang MY, Tanino Y, Vidova V, Kinsella MG, Chan CK, Johnson PY, et al. Reprint of: A rapid increase in macrophage-derived versican and hyaluronan in infectious lung disease. Matrix Biol. 2014; 35:162–173. [PubMed: 24727035]

263. Nandadasa S, Foulcer S, Apte SS. The multiple complex roles of versican and its proteolytic turnover by ADAMTS proteases during embryogenesis. Matrix Biol. 2014; 35:152–161. [PubMed: 24513039]

264. Foulcer SJ, Nelson CM, Quintero MV, Kubran B, Larkin J, Dours-Zimmermann MT, et al. Determinants of versican-V1 proteoglycan processing by the metalloproteinase ADAMTS5. J Biol Chem. 2014; 289:27859–27873. [PubMed: 25122765]
265. Keire PA, Bressler SL, Lemire JM, Edris B, Rubin BP, Rahmani M, et al. A role for versican in the development of leiomyosarcoma. J Biol Chem. 2014; 289:34089–34103. [PubMed: 25320080]

266. Mukhopadhyay A, Nikopoulos K, Maugeri A, de Brouwer APM, van Nouhuys CE, Boon CJF, et al. Erosive vitreoretinopathy and Wagner disease are caused by intronic mutations in CSPG2/Versican that result in an imbalance of splice variants. Invest Ophthalmol Vis Sci. 2006; 47:3565–3572. [PubMed: 16877430]

267. Rauch U, Karthikeyan L, Maurel P, Margolis RU, Margolis RK. Cloning and primary structure of neurocan, a developmentally regulated, aggregating chondroitin sulfate proteoglycan of brain. J Biol Chem. 1992; 267:19536–19547. [PubMed: 1326557]

268. Retzler C, Wiedemann H, Kulbe G, Rauch U. Structural and electron microscopic analysis of neurocan and recombinant neurocan fragments. J Biol Chem. 1996; 271:17107–17113. [PubMed: 8663259]

269. Davies JE, Tang X, Denning JW, Archibald SJ, Davies SJ. Decorin suppresses neurocan, brevican, phosphacan and NG2 expression and promotes axon growth across adult rat spinal cord injuries. Eur J Neurosci. 2004; 19:1226–1242. [PubMed: 15016081]

270. Yamaguchi Y. Brevican: a major proteoglycan in adult brain. Perspect Dev Neurobiol. 1996; 3:307–317. [PubMed: 9117262]

271. Yamada H, Watanabe K, Shimonaka M, Yamaguchi Y. Molecular cloning of brevican, a novel brain proteoglycan of the aggrecan/versican family. J Biol Chem. 1994; 269:10119–10126. [PubMed: 8144512]

272. Jaworski DM, Kelly GM, Hockfield S. BEHAB, a new member of the proteoglycan tandem repeat family of hyaluronan-binding proteins that is restricted to the brain. J Cell Biol. 1994; 125:495–509. [PubMed: 7512973]

273. Seidenbecher CI, Richter K, Rauch U, Fässler R, Garner CC, Gundelfinger ED. Brevican, a chondroitin sulfate proteoglycan of rat brain, occurs in secreted and cell surface glycosylphosphatidylinositol-anchored isofoms. J Biol Chem. 1995; 270:27206–27212. [PubMed: 7592978]

274. Frischknecht R, Seidenbecher CI. Brevican: a key proteoglycan in the perisynaptic extracellular matrix of the brain. Int J Biochem Cell Biol. 2012; 44:1051–1054. [PubMed: 22537913]

275. Iozzo, RV.; Goldoni, S.; Berendsen, A.; Young, MF. Small leucine-rich proteoglycans. In: Mecham, RP., editor. Extracellular matrix: an overview. Springer; 2011. p. 197-231.

276. Scholzen T, Solursh M, Suzuki S, Reiter R, Morgan JL, Buchberg AM, et al. The murine decorin. Complete cDNA cloning, genomic organization, chromosomal assignment and expression during organogenesis and tissue differentiation. J Biol Chem. 1994; 269:28720–28281. [PubMed: 7961765]

277. Iozzo RV. The family of the small leucine-rich proteoglycans: key regulators of matrix assembly and cellular growth. Crit Rev Biochem Mol Biol. 1997; 32:141–174. [PubMed: 9145286]

278. Zoeller JJ, Pintong W, Corby H, Goldoni S, Iozzo AE, Owens RT, et al. A central role for decorin during vertebrate convergent extension. J Biol Chem. 2009; 284:11728–11737. [PubMed: 19211552]

279. Iozzo RV. The biology of the small leucine-rich proteoglycans. Functional network of interactive proteins. J Biol Chem. 1999; 274:18843–18846. [PubMed: 10383378]

280. Iozzo RV, Karamanos N. Proteoglycans in health and disease: emerging concepts and future directions. FEBS J. 2010; 277:3863. [PubMed: 20812984]

281. Schaef er L, Iozzo RV. Biological functions of the small leucine-rich proteoglycans: from genetics to signal transduction. J Biol Chem. 2008; 283:21305–21309. [PubMed: 18463092]

282. Reed CC, Iozzo RV. The role of decorin in collagen fibrillogenesis and skin homeostasis. Glycoconj J. 2002; 19:249–255. [PubMed: 12975602]

283. Chen S, Birk DE. The regulatory roles of small leucine-rich proteoglycans in extracellular matrix assembly. FEBS J. 2013; 280:2120–2137. [PubMed: 23331954]

284. Reese SP, Underwood CJ, Weiss JA. Effects of decorin proteoglycan on fibrillogenesis, ultrastructure, and mechanics of type I collagen gels. Matrix Biol. 2013; 32:414–423. [PubMed: 23608680]
285. Dunkman AA, Buckley MR, Mienaltowski MJ, Adams SM, Thomas SJ, Satchell L, et al. Decorin expression is important for age-related changes in tendon structure and mechanical properties. Matrix Biol. 2013; 32:3–13. [PubMed: 23178232]

286. Chen SC, Young MF, Chakravarti S, Birk DE. Interclass small leucine-rich repeat proteoglycan interactions regulate collagen fibrillogenesis and corneal stromal assembly. Matrix Biol. 2014; 35:103–111. [PubMed: 2447998]

287. Iozzo RV, Moscetello D, McQuillan DJ, Eichstetter I. Decorin is a biological ligand for the epidermal growth factor receptor. J Biol Chem. 1999; 274:4489–4492. [PubMed: 9986878]

288. Goldoni S, Humphries A, Nyström A, Sattar S, Owens RT, McQuillan DJ, et al. Decorin is a novel antagonistic ligand of the Met receptor. J Cell Biol. 2009; 185:743–754. [PubMed: 19433454]

289. Morcavallo A, Buraschi S, Xu S-Q, Belfiore A, Schaefer L, Iozzo RV, et al. Decorin differentially modulates the activity of insulin receptor isoform A ligands. Matrix Biol. 2014; 35:82–90. [PubMed: 24389353]

290. Horváth Z, Koválszky I, Fullár A, Kiss K, Schaff Z, Iozzo RV, et al. Decorin deficiency promotes hepatic carcinogenesis. Matrix Biol. 2014; 35:194–205. [PubMed: 24361483]

291. Merline R, Moreth K, Beckmann J, Nastase MV, Zeng-Brouwers J, Tralhão JG, et al. Signaling by the matrix proteoglycan decorin controls inflammation and cancer through PDCD4 and microRNA-21. Sci Signal. 2011; 4:ra75. [PubMed: 22087031]

292. Schaefer L, Iozzo RV. Small leucine-rich proteoglycans, at the crossroad of cancer growth and inflammation. Curr Opin Genet Dev. 2012; 22:56–57. [PubMed: 22326829]

293. Goldoni S, Owens RT, McQuillan DJ, Shriver Z, Sasisekharan R, Birk DE, et al. Biologically active decorin is a monomer in solution. J Biol Chem. 2004; 279:6606–6612. [PubMed: 14660661]

294. Iozzo RV, Schaefer L. Proteoglycans in health and disease: novel regulatory signaling mechanisms evoked by the small leucine-rich proteoglycans. FEBS J. 2010; 277:3864–3875. [PubMed: 20840584]

295. Goldoni S, Iozzo RV. Tumor microenvironment: modulation by decorin and related molecules harboring leucine-rich tandem motifs. Int J Cancer. 2008; 123:2473–2479. [PubMed: 18798267]

296. Iozzo RV. Proteoglycans and neoplasia. Cancer Metastasis Rev. 1988; 7:39–50. [PubMed: 3293831]

297. Neill T, Schaefer L, Iozzo RV. An oncosuppressive role for decorin. Mol Cell Oncol. 2015 [in press].

298. Scott PG, McEwan PA, Dodd CM, Bergmann EM, Bishop PN, Bella J. Crystal structure of the dimeric protein core of decorin, the archetypal small leucine-rich repeat proteoglycan. Proc Natl Acad Sci U S A. 2004; 101:15633–15638. [PubMed: 15501918]

299. Park H, Huxley-Jones J, Boot-Handford RP, Bishop PN, Attwood TK, Bella J. LRRCE: a leucine-rich repeat cysteine capping motif unique to the chordate lineage. BMC Genomics. 2008; 9:599. [PubMed: 19077264]

300. McEwan PA, Scott PG, Bishop PN, Bella J. Structural correlations in the family of small leucine-rich repeat proteins and proteoglycans. J Struct Biol. 2006; 155:294–305. [PubMed: 16884925]

301. Bredrup C, Knappskog PM, Majewski J, Rødahl E, Boman H. Congenital stromal dystrophy of the cornea caused by a mutation in the decorin gene. Investig Ophthalmol Vis Sci. 2005; 46:420–426. [PubMed: 15671264]

302. Chen S, Sun M, Meng X, Iozzo RV, Kao WWY, Birk DE. Pathophysiological mechanisms of autosomal dominant congenital stromal corneal dystrophy. C-terminal-truncated decorin results in abnormal matrix assembly and altered expression of small leucine-rich proteoglycans. Am J Pathol. 2011; 179:2409–2419. [PubMed: 21893019]

303. Chen A, Sun M, Iozzo RV, Kao WW-Y, Birk DE. Intracellularly-retained decorin lacking the C-terminal ear repeat causes ER stress. A cell-based etiological mechanism for congenital stromal corneal dystrophy. Am J Pathol. 2013; 183:247–256. [PubMed: 23685109]

304. Scott PG, Grossmann JG, Dodd CM, Sheehan JK, Bishop PN. Light and X-ray scattering show decorin to be a dimer in solution. J Biol Chem. 2003; 278:18353–18359. [PubMed: 12601001]
305. Santra M, Reed CC, Iozzo RV. Decorin binds to a narrow region of the epidermal growth factor (EGF) receptor, partially overlapping with but distinct from the EGF-binding epitope. J Biol Chem. 2002; 277:35671–35681. [PubMed: 12105206]

306. Kalamajski S, Aspberg A, Oldberg Å. The decorin sequence SYIRIADTNIT binds collagen type I. J Biol Chem. 2007; 282:16062–16067. [PubMed: 17426031]

307. Kalamajski S, Oldberg Å. The role of small leucine-rich proteoglycans in collagen fibrillogenesis. Matrix Biol. 2010; 29:248–253. [PubMed: 20080181]

308. Islam M, Gor J, Perkins SJ, Ishikawa Y, Bächinger HS, Hohenester E. The concave face of decorin mediates reversible dimerization and collagen binding. J Biol Chem. 2013; 288:35526–35533. [PubMed: 24169694]

309. Vogel KG, Paulsson M, Heinegård D. Specific inhibition of type I and type II collagen fibrillogenesis by the small proteoglycan of tendon. Biochem J. 1984; 223:587–597. [PubMed: 6439184]

310. Danielson KG, Baribault H, Holmes DF, Graham H, Kadler KE, Iozzo RV. Targeted disruption of decorin leads to abnormal collagen fibril morphology and skin fragility. J Cell Biol. 1997; 136:729–743. [PubMed: 9024701]

311. Scott JE, Orford CR. Dermatan sulphate-rich proteoglycan associates with rat tail-tendon collagen at the d band in the gap region. Biochem J. 1981; 197:213–216. [PubMed: 7317031]

312. Scott JE. Proteoglycan–fibrillar collagen interactions. Biochem J. 1988; 252:313–323. [PubMed: 3046606]

313. Keene DR, San Antonio JD, Mayne R, McQuillan DJ, Sarris G, Santoro SA, et al. Decorin binds near the C terminus of type I collagen. J Biol Chem. 2000; 275:21801–21804. [PubMed: 10823816]

314. Rühland C, Schönherr E, Robenek H, Hansen U, Iozzo RV, Bruckner P, et al. The glycosaminoglycan chain of decorin plays an important role in collagen fibril formation at the early stages of fibrillogenesis. FEBS J. 2007; 274:4246–4255. [PubMed: 17651433]

315. Raspanti M, Violoa M, Forlino A, Tenni R, Gruppi C, Tira ME. Glycosaminoglycans show a specific periodic interaction with type I collagen fibrils. J Struct Biol. 2008; 164:134–139. [PubMed: 18664384]

316. Schaefer L. Small leucine-rich proteoglycans in kidney disease. J Am Soc Nephrol. 2011; 22:1200–1207. [PubMed: 21719787]

317. Nikitovic D, Aggelidakis J, Young MF, Iozzo RV, Karamanos NK, Tzanakakis GN. The biology of small leucine-rich proteoglycans in bone pathophysiology. J Biol Chem. 2012; 287:33926–33933. [PubMed: 22879588]

318. Baghy K, Iozzo RV, Kovalszky I. Decorin–TGFβ axis in hepatic fibrosis and cirrhosis. J Histochem Cytochem. 2012; 60:262–268. [PubMed: 22260996]

319. Feugaing DDS, Götte M, Viola M. More than matrix: the multifaceted role of decorin in cancer. Eur J Cell Biol. 2013; 92:1–11. [PubMed: 23058688]

320. Merline, R.; Nastase, MV.; Iozzo, RV.; Schaefer, L. Small leucine-rich proteoglycans: multifunctional signaling effectors. In: Karamanos, N., editor. Extracellular matrix: pathobiology and signaling. Berlin: Walter de Gruyter Gmbh and Co.; 2012. p. 185-196.

321. Dellett M, Hu W, Papadaki V, Ohnuma S. Small leucine rich proteoglycan family regulates multiple signalling pathways in neural development and maintenance. Dev Growth Differ. 2012; 54:327–340. [PubMed: 22524604]

322. Karamanos NK, Tzanakakis GN. Glycosaminoglycans: from ‘cellular glue’ to novel therapeutical agents. Curr Opin Pharmacol. 2012; 12:220–222. [PubMed: 22325837]

323. Nastase MV, Iozzo RV, Schaefer L. Key roles for the small leucine-rich proteoglycans in renal and pulmonary pathophysiology. Biochim Biophys Acta. 2014; 1840:2460–2470. [PubMed: 24508120]

324. Skandalis SS, Afratis N, Smirlaki G, Nikitovic D, Theocharis AD, Tzanakakis GN, et al. Cross-talk between estradiol receptor and EGFR/IGF-IR signaling pathways in estrogen-responsive breast cancers: focus on the role and impact of proteoglycans. Matrix Biol. 2014; 35:182–193. [PubMed: 24063949]

Matrix Biol. Author manuscript; available in PMC 2016 May 06.
325. Takanosu M, Boyd TC, Le GM, Henry SP, Zhang Y, Bishop PN, et al. Structure, chromosomal location, and tissue-specific expression of the mouse opticin gene. Invest Ophthalmol Vis Sci. 2001; 42:2202–2210. [PubMed: 11527931]

326. Tasheva ES, Klocke B, Conrad GW. Analysis of transcriptional regulation of the small leucine rich proteoglycans. Mol Vis. 2004; 10:758–772. [PubMed: 15496828]

327. Krusius T, Ruoslahti E. Primary structure of an extracellular matrix proteoglycan core protein deduced from cloned cDNA. Proc Natl Acad Sci U S A. 1986; 83:7683–7687. [PubMed: 3484330]

328. Ruoslahti E. Structure and biology of proteoglycans. Annu Rev Cell Biol. 1988; 4:229–255. [PubMed: 3143379]

329. Yang VWC, LaBrenz SR, Rosenberg LC, McQuillan D, Höök M. Decorin is a Zn$^{2+}$ metalloprotein. J Biol Chem. 1999; 274:12454–12460. [PubMed: 10212220]

330. Dugan TA, Yang VWC, McQuillan DJ, Höök M. Decorin binds fibrinogen in a Zn$^{2+}$-dependent interaction. J Biol Chem. 2003; 278:13655–13662. [PubMed: 12582160]

331. Henninger HB, Maas SA, Underwood CJ, Whitaker RT, Weiss JA. Spatial distribution and orientation of dermatan sulfate in human medial collateral ligament. J Struct Biol. 2006; 158:33–45. [PubMed: 17150374]

332. Jungmann O, Nikolovska K, Stock C, Schulz J-N, Eckes B, Riethmüller C, et al. The dermatan sulfate proteoglycan decorin modulates α2β1 integrin and vimentin intermediate filament system during collagen synthesis. PLoS One. 2012; 7:e50809. [PubMed: 23226541]

333. Nikolovska K, Renke JK, Jungmann O, Grobe K, Iozzo RV, Zamfir AD, et al. A decorin-deficient matrix affects skin chondroitin/dermatan sulfate levels and keratinocyte function. Matrix Biol. 2014; 35:91–102. [PubMed: 24447999]

334. Dunkman AA, Buckley MR, Mienaltowski MJ, Adams SM, Thomas SJ, Kumar A, et al. The injury response of aged tendons in the absence of biglycan and decorin. Matrix Biol. 2014; 35:232–238. [PubMed: 24157578]

335. Vesentini S, Redaelli A, Montevacchi FM. Estimation of the binding force of the collagen molecule-decorin core protein complex in collagen fibril. J Biomech. 2005; 38:433–443. [PubMed: 15652541]

336. Danielson KG, Fazzio A, Cohen I, Cannizzaro LA, Eichstetter I, Iozzo RV. The human decorin gene: intron–exon organization, discovery of two alternatively spliced exons in the 5′ untranslated region, and mapping of the gene to chromosome 12q23. Genomics. 1993; 15:146–160. [PubMed: 8432526]

337. Santra M, Danielson KG, Iozzo RV. Structural and functional characterization of the human decorin gene promoter. A homopurine–homopyrimidine S1 nuclease-sensitive region is involved in transcriptional control. J Biol Chem. 1994; 269:579–587. [PubMed: 8276854]

338. Mauviel A, Korang K, Santra M, Tewari D, Uitto J, Iozzo RV. Identification of a bimodal regulatory element encompassing a canonical AP-1 binding site in the proximal promoter region of the human decorin gene. J Biol Chem. 1996; 271:24824–24829. [PubMed: 8798756]

339. Mauviel A, Santra M, Chen YQ, Uitto J, Iozzo RV. Transcriptional regulation of decorin gene expression. Induction by quiescence and repression by tumor necrosis factor-α. J Biol Chem. 1995; 270:11692–11700. [PubMed: 7744809]

340. Iozzo RV, Danielson KG. Transcriptional and posttranscriptional control of proteoglycan gene expression. Prog Nucleic Acids Res Mol Biol. 1999; 62:19–53.

341. Byers PH, Murray ML. Ehlers–Danlos syndrome: a showcase of conditions that lead to understanding matrix biology. Matrix Biol. 2014; 33:10–15. [PubMed: 23920413]

342. Rudnicka L, Varga J, Christiano AM, Iozzo RV, Jimenez SA, Uitto J. Elevated expression of type VII collagen in the skin of patients with systemic sclerosis. J Clin Invest. 1994; 93:1709–1715. [PubMed: 7512991]

343. Brown EL, Wooten RM, Johnson BJ, Iozzo RV, Smith A, Dolan MC, et al. Resistance to Lyme disease in decorin-deficient mice. J Clin Invest. 2001; 107:845–852. [PubMed: 11285303]

344. Liang FT, Wang T, Brown EL, Iozzo RV, Fikrig E. Protective niche for Borrelia burgdorferi to evade humoral immunity. Am J Pathol. 2004; 165:977–985. [PubMed: 15331421]
345. Fust A, LeBellego F, Iozzo RV, Roughley PJ, Ludwig MS. Alterations in lung mechanics in decorin deficient mice. Am J Physiol Lung Cell Mol Physiol. 2005; 288:L159–L166. [PubMed: 15447936]

346. Marchica CL, Pinelli V, Borges M, Zummer J, Narayanan V, Iozzo RV, et al. A role for decorin in a murine model of allergen-induced asthma. Am J Physiol Lung Cell Mol Physiol. 2011; 300:S63–S87.

347. Williams KJ, Qiu G, Usui HK, Dunn SR, McCue P, Bottinger E, et al. Decorin deficiency enhances progressive nephropathy in diabetic mice. Am J Pathol. 2007; 171:1441–1450. [PubMed: 17884968]

348. Merline R, Lazaroski S, Babelova A, Tsalastra-Greul W, Pfeilschifter J, Schluter KD, et al. Decorin deficiency in diabetic mice: aggravation of nephropathy due to overexpression of profibrotic factors, enhanced apoptosis and mononuclear cell infiltration. J Physiol Pharmacol. 2009; 60(Suppl 4):5–13. [PubMed: 20083846]

349. Schaefer L, Macakova K, Rasliik I, Micegova M, Grone HJ, Schönherr E, et al. Absence of decorin adversely influences tubulointerstitial fibrosis of the obstructed kidney by enhanced apoptosis and increased inflammatory reaction. Am J Pathol. 2002; 160:1181–1191. [PubMed: 11891213]

350. Schaefer L, Mihalik D, Babelova A, Krzyzankova M, Grone HJ, Iozzo RV, et al. Regulation of fibrillin-1 by biglycan and decorin is important for tissue preservation in the kidney during pressure-induced injury. Am J Pathol. 2004; 165:383–396. [PubMed: 15277214]

351. Weis SM, Zimmermann KD, Shah M, Covell JW, Omens JH, Ross J Jr, et al. A role for decorin in the remodeling of myocardial infarction. Matrix Biol. 2005; 24:313–324. [PubMed: 15949932]

352. Zhang G, Chen S, Goldoni S, Calder BW, Simpson HC, Owens RT, et al. Genetic evidence for the coordinated regulation of collagen fibrillogenesis in the cornea by decorin and biglycan. J Biol Chem. 2009; 284:8888–8897. [PubMed: 19136671]

353. Zhang G, Ezura Y, Chervoneva I, Robinson PS, Beason DP, Carine ET, et al. Decorin regulates assembly of collagen fibrils and acquisition of biomechanical properties during tendon development. J Cell Biochem. 2006; 98:1436–1449. [PubMed: 16518859]

354. Robinson PS, Huang TF, Kazem E, Iozzo RV, Birk DE, Soslowsky LJ. Influence of decorin and biglycan on mechanical properties of multiple tendons in knockout mice. J Biomech Eng. 2005; 127:181–185. [PubMed: 15868800]

355. Robinson PS, Lin TW, Jawad AF, Iozzo RV, Soslowsky LJ. Investigating tendon fascicle structure–function relationship in a transgenic age mouse model using multiple regression models. Ann Biomed Eng. 2004; 32:924–931. [PubMed: 15298430]

356. Elliott DM, Robinson PS, Gimbel JA, Sarver JJ, Abboud JA, Iozzo RV, et al. Effect of altered matrix proteins on quasilinear viscoelastic properties in transgenic mouse tail tendons. Ann Biomed Eng. 2003; 31:599–605. [PubMed: 12757203]

357. Goldberg M, Septier D, Rapoport O, Iozzo RV, Young MF, Ameye LG. Targeted disruption of two small leucine-rich proteoglycans, biglycan and decorin, exerts divergent effects on enamel and dentin formation. Calcif Tissue Int. 2005; 77:297–310. [PubMed: 16283572]

358. Haruyama N, Sreenath TL, Suzuki S, Yao X, Wang Z, Wang Y, et al. Genetic evidence for key roles of decorin and biglycan in dentin mineralization. Matrix Biol. 2009; 28:129–136. [PubMed: 19379665]

359. Häkkinen L, Strassburger S, Kahari VM, Scott PG, Eichstetter I, Iozzo RV, et al. A role for decorin in the structural organization of periodontal ligament. Lab Invest. 2000; 80:1869–1880. [PubMed: 11140699]

360. Baghy K, Deszó K, László V, Fullár A, Péterfia B, Paku S, et al. Ablation of the decorin gene enhances experimental hepatic fibrosis and impairs hepatic healing in mice. Lab Invest. 2011; 91:439–451. [PubMed: 20956977]

361. Baghy K, Horváth Z, Regös E, Kiss K, Schaff Z, Iozzo RV, et al. Decorin interferes with platelet-derived growth factor receptor signaling in experimental hepatocarcinogenesis. FEBS J. 2013; 280:2150–2164. [PubMed: 23448253]

362. Horvath Z, Kovalszky I, Fullar A, Kiss K, Schaff Z, Iozzo RV, et al. Decorin deficiency promotes hepatic carcinogenesis. Matrix Biol. 2014; 35:194–205. [PubMed: 24361483]
363. Seidler DG, Schaefer L, Robenek H, Iozzo RV, Kresse H, Schönherr E. A physiologic three-dimensional cell culture system to investigate the role of decorin in matrix organisation and cell survival. Biochem Biophys Res Commun. 2005; 332:1162–1170. [PubMed: 15949467]

364. Ferdous Z, Lazaro LD, Iozzo RV, Höök M, Grande-Allen KJ. Influence of cyclic strain and decorin deficiency on 3D cellularized collagen matrices. Biomaterials. 2008; 29:2740–2748. [PubMed: 18394699]

365. Calmus ML, Mack sound EE, Tucker R, Iozzo RV, Lechner BE. A mouse model of spontaneous preterm birth based on the genetic ablation of biglycan and decorin. Reproduction. 2011; 142:183–194. [PubMed: 21502335]

366. Wu Z, Aron AW, Mack sound EE, Iozzo RV, Hai C-M, Lechner BE. Uterine dysfunction in biglycan and decorin deficient mice leads to dystocia during parturition. PLoS One. 2012; 7:e29627. [PubMed: 22253749]

367. Wu Z, Horgan CE, Carr O, Owens RT, Iozzo RV, Lechner BE. Biglycan and decorin differentially regulate signaling in the fetal membranes. Matrix Biol. 2014; 35:266–275. [PubMed: 24373743]

368. Järveläinen H, Puolakkainen P, Pakkanen S, Brown EL, Höök M, Iozzo RV, et al. A role for decorin in cutaneous wound healing and angiogenesis. Wound Repair Regen. 2006; 14:443–452. [PubMed: 16939572]

369. Grant DS, Yenisey C, Rose RW, Tootell M, Santra M, Iozzo RV. Decorin suppresses tumor cell-mediated angiogenesis. Oncogene. 2002; 21:4765–4777. [PubMed: 12101415]

370. Schönherr E, Sunderkotter C, Schaefer L, Thanos S, Grässel S, Oldberg Å, et al. Decorin deficiency leads to impaired angiogenesis in injured mouse cornea. J Vasc Res. 2004; 41:499–508. [PubMed: 15528932]

371. Neill T, Painter H, Buraschi S, Owens RT, Lisanti MP, Schaefer L, et al. Decorin antagonizes the angiogenic network. Concurrent inhibition of Met, hypoxia inducible factor-1α and vascular endothelial growth factor A and induction of thrombospondin-1 and TIMP3. J Biol Chem. 2012; 287:5492–5506. [PubMed: 22194599]

372. Neill T, Jones HR, Crane-Smith Z, Owens RT, Schaefer L, Iozzo RV. Decorin induces rapid secretion of thrombospondin-1 in basal breast carcinoma cells via inhibition of Ras homolog gene family, member A/Rho-associated coiled-coil containing protein kinase 1. FEBS J. 2013; 280:2353–2368. [PubMed: 23350987]

373. Järveläinen H, Saino A, Wight TN. Pivotal role for decorin in angiogenesis. Matrix Biol. 2015 [in press].

374. Seidler DG, Mohamed NA, Bocian C, Stadtmann A, Hern mann S, Schäfers K, et al. The role for decorin in delayed-type hypersensitivity. J Immunol. 2011; 187:6108–6199. [PubMed: 22043007]

375. Bocian C, Urbanowicz AK, Owens RT, Iozzo RV, Gotte M, Seidler DG. Decorin potentiates interferon-gamma activity in a model of allergic inflammation. J Biol Chem. 2013; 288:12699–12711. [PubMed: 23460644]

376. Ferdous Z, Peterson SB, Tseng H, Anderson DK, Iozzo RV, Grande-Allen KJ. A role for decorin in controlling proliferation, adhesion, and migration of murine embryonic fibroblasts. J Biomed Mater Res A. 2010; 93:419–428. [PubMed: 19569212]

377. Bi Y, Stuel tens CH, Kiits T, Wadhwa S, Iozzo RV, Robey PG, et al. Extracellular matrix proteoglycans control the fate of bone marrow stromal cells. J Biol Chem. 2005; 280:30481–30489. [PubMed: 15964849]

378. Ichii M, Frank MB, Iozzo RV, Kincade PW. The canonical Wnt pathway shapes niches supportive of hematopoietic stem/progenitor cells. Blood. 2012; 119:1683–1692. [PubMed: 22117039]

379. Kim J-H, Ko JM, Lee I, Kim JY, Kim MJ, Tchah H. A novel mutation of the decorin gene identified in a Korean family with congenial hereditary stromal dystrophy. Cornea. 2011; 30:1473–1477. [PubMed: 21993463]

380. Chen S, Sun M, Iozzo RV, Kao WW, Birk DE. Intracellularly-retained decorin lacking the C-terminal ear repeat causes ER stress: a cell-based etiological mechanism for congenital stromal corneal dystrophy. Am J Pathol. 2013; 183:247–256. [PubMed: 23685109]

381. Yamaguchi Y, Ruoslahti E. Expression of human proteoglycan in Chinese hamster ovary cells inhibits cell proliferation. Nature. 1988; 336:244–246. [PubMed: 3194009]
382. Yamaguchi Y, Mann DM, Ruoslahti E. Negative regulation of transforming growth factor-β by the proteoglycan decorin. Nature. 1990; 346:281–284. [PubMed: 2374594]

383. Adany R, Heimer R, Caterson B, Sorrell JM, Iozzo RV. Altered expression of chondroitin sulfate proteoglycan in the stroma of human colon carcinoma. Hypomethylation of PG-40 gene correlates with increased PG-40 content and mRNA levels. J Biol Chem. 1990; 265:11389–11396. [PubMed: 2162845]

384. Adany R, Iozzo RV. Altered methylation of versican proteoglycan gene in human colon carcinoma. Biochem Biophys Res Commun. 1990; 171:1402–1413. [PubMed: 2222452]

385. Santra M, Skorski T, Calabretta B, Lattime EC, Iozzo RV. De novo decorin gene expression suppresses the malignant phenotype in human colon cancer cells. Proc Natl Acad Sci U S A. 1995; 92:7016–7020. [PubMed: 7624361]

386. Santra M, Mann DM, Mercer EW, Skorski T, Calabretta B, Iozzo RV. Ectopic expression of decorin protein core causes a generalized growth suppression in neoplastic cells of various histogenetic origin and requires endogenous p21, an inhibitor of cyclin-dependent kinases. J Clin Invest. 1997; 100:149–157. [PubMed: 9202067]

387. De Luca A, Santra M, Baldi A, Giordano A, Iozzo RV. Decorin-induced growth suppression is associated with upregulation of p21, an inhibitor of cyclin-dependent kinases. J Biol Chem. 1996; 271:18961–18965. [PubMed: 8702560]

388. Moscatello DK, Santra M, Mann DM, McQuillan DJ, Wong AJ, Iozzo RV. Decorin suppresses tumor cell growth by activating the epidermal growth factor receptor. J Clin Invest. 1998; 101:406–412. [PubMed: 9435313]

389. Patel S, Santra M, McQuillan DJ, Iozzo RV, Thomas AP. Decorin activates the epidermal growth factor receptor and elevates cytosolic Ca²⁺ in A431 cells. J Biol Chem. 1998; 273:3121–3124. [PubMed: 9452417]

390. Csordás G, Santra M, Reed CC, Eichstetter I, McQuillan DJ, Gross D, et al. Sustained down-regulation of the epidermal growth factor receptor by decorin. A mechanism for controlling tumor growth in vivo. J Biol Chem. 2000; 275:32879–32887. [PubMed: 10913155]

391. Hu Y, Sun H, Owens RT, Wu J, Chen YQ, Berquin IM, et al. Decorin suppresses prostate tumor growth through inhibition of epidermal growth factor and androgen receptor pathways. Neoplasia. 2009; 11:1042–1053. [PubMed: 19794963]

392. Nash MA, Loercher AE, Freedman RS. In vitro growth inhibition of ovarian cancer cells by decorin: synergism of action between decorin and carboplatin. Cancer Res. 1999; 59:6192–6196. [PubMed: 10626812]

393. Zhu J-X, Goldoni S, Bix G, Owens RA, McQuillan D, Reed CC, et al. Decorin evokes protracted internalization and degradation of the EGF receptor via caveolar endocytosis. J Biol Chem. 2005; 280:32468–32479. [PubMed: 15994311]

394. Santra M, Eichstetter I, Iozzo RV. An anti-oncogenic role for decorin: downregulation of ErbB2 leads to growth suppression and cytodifferentiation of mammary carcinoma cells. J Biol Chem. 2000; 275:35153–35161. [PubMed: 10942781]

395. Buraschi S, Pal N, Tyler-Rubinstein N, Owens RT, Neill T, Iozzo RV. Decorin antagonizes Met receptor activity and downregulates β-cat, Cdkn1a, and Myc levels. J Biol Chem. 2010; 285:42075–42085. [PubMed: 20974860]

396. Schönherr E, Sunderkötter C, Iozzo RV, Schaefer L. Decorin, a novel player in the insulin-like growth factor system. J Biol Chem. 2005; 280:15767–15772. [PubMed: 15701628]

397. Iozzo RV, Buraschi S, Genua M, Xu S-Q, Solomides CC, Peiper SC, et al. Decorin antagonizes IGF receptor I (IGF-IR) function by interfering with IGF-IR activity and attenuating downstream signaling. J Biol Chem. 2011; 286:34712–34721. [PubMed: 21840990]

398. Lala N, Gannareddy VG, Cloutier-Bosworth A, Lala PK. Mechanisms in decorin regulation of vascular endothelial growth factor-induced human trophoblast migration and acquisition of endothelial phenotype. Biol Reprod. 2012; 87:1–14. [article 59].

399. Troup S, Njue C, Kliever EV, Parisien M, Roskelley C, Chakravarti S, et al. Reduced expression of the small leucine-rich proteoglycans, lumican, and decorin is associated with poor outcome in node-negative invasive breast cancer. Clin Cancer Res. 2003; 9:207–214. [PubMed: 12538471]
400. Goldoni S, Seidler DG, Heath J, Fassan M, Baffa R, Thakur ML, et al. An anti-metastatic role for decorin in breast cancer. Am J Pathol. 2008; 173:844–855. [PubMed: 18688028]

401. Gu Y, Zhang S, Wu Q, Xu S, Cui Y, Yang Z, et al. Differential expression of decorin, EGFR and cyclin D1 during mammary gland carcinogenesis in TA2 mice with spontaneous breast cancers. J Exp Clin Cancer Res. 2010; 29:6. [PubMed: 20092659]

402. Bozoky B, Savchenko A, Guven H, Ponten F, Klein G, Szekely L. Decreased decorin expression in the tumor microenvironment. Cancer Med. 2014; 3:485–491. [PubMed: 24643138]

403. Lieveld M, Bodson E, De BG, Nouman B, Cleton-Jansen AM, Korsching E, et al. Gene expression profiling of giant cell tumor of bone reveals downregulation of extracellular matrix components decorin and lumican associated with lung metastasis. Virchows Arch. 2014; 465:703–713. [PubMed: 25304290]

404. Königer J, Giese NA, di Mola FF, Berberat P, Giese T, Esposito I, et al. Overexpressed decorin in pancreatic cancer: potential tumor growth inhibition and attenuation of chemotherapeutic action. Clin Cancer Res. 2004; 10:4776–4783. [PubMed: 15269152]

405. Stock C, Jungmann O, Seidler DG. Decorin and chondroitin-6 sulfate inhibit B16V melanoma cell migration and invasion by cellular acidification. J Cell Physiol. 2011; 226:2641–2650. [PubMed: 21792923]

406. Kristensen IB, Pedersen L, Ro TD, Christensen JH, Lyng MB, Rasmussen LM, et al. Decorin is down-regulated in multiple myeloma and MGUS bone marrow plasma and inhibits HGF-induced myeloma plasma cell viability and migration. Eur J Haematol. 2013; 91:196–200. [PubMed: 23607294]

407. Matsumine A, Shintani K, Kusuzaki K, Matsubara T, Satonaka H, Wakabayashi T, et al. Expression of decorin, a small leucine-rich proteoglycan, as a prognostic factor in soft tissue tumors. J Surg Oncol. 2007; 96:411–418. [PubMed: 17579351]

408. Henke A, Grace OC, Ashley GR, Stewart GD, Riddick ACP, Yeun H, et al. Stromal expression of decorin, semaphorin6D, SPARC, Sprouty 1 and Tsukushi in developing prostate and decreased levels of decorin in prostate cancer. PLoS One. 2012; 7:e4251.

409. Sanchez-Carbayo M, Socci ND, Lozano J, Saint F, Cordon-Cardo C. Defining molecular profiles of poor outcome in patients with invasive bladder cancer using oligonucleotide microarrays. J Clin Oncol. 2006; 24:778–789. [PubMed: 16432078]

410. Dyrsjköt L, Kruhoffer M, Thykjaer T, Marcussen N, Jensen JL, Møller K, et al. Gene expression in the urinary bladder: a common carcinoma in situ gene expression signature exists disregarding histopathological classification. Cancer Res. 2004; 64:4040–4048. [PubMed: 15173019]

411. Sainio A, Nyman M, Lund R, Vuorikoski S, Boström P, Laato M, et al. Lack of decorin expression by human bladder cancer cells offers new tools in the therapy of urothelial malignancies. PLoS One. 2013; 8:e76190. [PubMed: 24146840]

412. Duncan MB. Extracellular matrix transcriptome dynamics in hepatocellular carcinoma. Matrix Biol. 2013; 32:393–398. [PubMed: 23727079]

413. Boström P, Sainio A, Kakko T, Savontaus M, Söderström M, Järveläinen H. Localization of decorin gene expression in normal human breast tissue and in benign and malignant tumors of the human breast. Histochem Cell Biol. 2013; 139:161–171. [PubMed: 23007289]

414. Neill T, Schaefer L, Iozzo RV. Decorin, a guardian from the matrix. Am J Pathol. 2012; 181:380–387. [PubMed: 22735579]

415. Bi X, Tong C, Dokendorf A, Banroft L, Gallagher L, Guzman-Hartman G, et al. Genetic deficiency of decorin causes intestinal tumor formation through disruption of intestinal cell maturation. Carcinogenesis. 2008; 29:1435–1440. [PubMed: 18550571]

416. Bi X, Pohl NM, Yang GR, Gou Y, Guzman G, Kajdacsy-Balla A, et al. Decorin-mediated inhibition of colorectal cancer growth and migration is associated with E-cadherin in vitro and in mice. Carcinogenesis. 2012; 33:326–330. [PubMed: 22159220]

417. Iozzo RV, Chakrani F, Perrotti D, McQuillan DJ, Skorski T, Calabretta B, et al. Cooperative action of germline mutations in decorin and p53 accelerates lymphoma tumorigenesis. Proc Natl Acad Sci U S A. 1999; 96:3092–3097. [PubMed: 10077642]

418. Reed CC, Waterhouse A, Kirby S, Kay P, Owens RA, McQuillan DJ, et al. Decorin prevents metastatic spreading of breast cancer. Oncogene. 2005; 24:1104–1110. [PubMed: 15690056]
419. Reed CC, Gauldie J, Iozzo RV. Suppression of tumorigenicity by adenovirus-mediated gene transfer of decorin. Oncogene. 2002; 21:3688–3695. [PubMed: 12032837]

420. Tralhão JG, Schaefer L, Micegova M, Evaristo C, Schönherr E, Kayal S, et al. In vivo selective and distant killing of cancer cells using adenovirus-mediated decorin gene transfer. FASEB J. 2003; 17:464–466. [PubMed: 12631584]

421. Seidler DG, Goldoni S, Agnew C, Cardi C, Thakur ML, Owens RA, et al. Decorin protein core inhibits in vivo cancer growth and metabolism by hindering epidermal growth factor receptor function and triggering apoptosis via caspase-3 activation. J Biol Chem. 2006; 281:26408–26418. [PubMed: 16835231]

422. Buraschi S, Neill T, Owens RT, Iniguez LA, Purkins G, Vadigepalli R, et al. Decorin protein core affects the global gene expression profile of the tumor microenvironment in a triple-negative orthotopic breast carcinoma xenograft model. PLoS One. 2012; 7:e45559. [PubMed: 23029096]

423. Li X, Pennisi A, Yaccoby S. Role of decorin in the antitumor effects of osteoblasts. Blood. 2008; 112:159–168. [PubMed: 18436739]

424. Xu W, Neill T, Yang Y, Hu Z, Cleveland E, Wu Y, et al. The systemic delivery of an oncolytic adenovirus expressing decorin inhibits bone metastasis in a mouse model of human prostate cancer. Gene Ther. 2015 [in press].

425. Buraschi S, Neill T, Goyal A, Poluzzi C, Smythies J, Owens RT, et al. Decorin causes autophagy in endothelial cells via Peg3. Proc Natl Acad Sci U S A. 2013; 110:E2582–E2591. [PubMed: 23798385]

426. Goyal A, Neill T, Owens RT, Schaefer L, Iozzo RV. Decorin activates AMPK, an energy sensor kinase, to induce autophagy in endothelial cells. Matrix Biol. 2014; 34:46–54. [PubMed: 24472739]

427. Neill T, Schaefer L, Iozzo RV. Instructive roles of extracellular matrix on autophagy. Am J Pathol. 2014; 184:2146–2153. [PubMed: 24976620]

428. Wu L-C, Wu D-C, Huang C-C, Lin H-S, Chen Y-K, Tsai H-J, et al. Plasma decorin predicts the presence of esophageal squamous cell carcinoma. Int J Cancer. 2010; 127:2138–2146. [PubMed: 20143390]

429. Bolton K, Segal D, McMillan J, Jowett J, Heilbronn L, Abberton K, et al. Decorin is a secreted protein associated with obesity and type 2 diabetes. Int J Obes. 2008; 32:1113–1121.

430. Xu Y-Z, Zhang Y-H, Zhang Y-W, Hong B, Liu J-M. Dynamic reduction of plasma decorin following ischemic stroke: a pilot study. Neurochem Res. 2012; 37:1843–1848. [PubMed: 22678721]

431. Fisher LW, Termine JD, Young MF. Deduced protein sequence of bone small proteoglycan I (biglycan) shows homology with proteoglycan II (decorin) and several nonconnective tissue proteins in a variety of species. J Biol Chem. 1989; 264:4571–4576. [PubMed: 2647739]

432. Fisher LW, Heegaard A-M, Vetter U, Vogel W, Just W, Termine JD, et al. Human biglycan gene. Putative promoter, intron–exon junctions, and chromosomal localization. J Biol Chem. 1991; 266:14371–14377. [PubMed: 1860845]

433. Wegrowski Y, Pillarisetti J, Danielson KG, Suzuki S, Iozzo RV. The murine biglycan: complete cDNA cloning, genomic organization, promoter function and expression. Genomics. 1995; 30:8–17. [PubMed: 8595907]

434. Hildebrand A, Romaris M, Rasmussen LM, Heinegard D, Twardzik DR, Border WA, et al. Interaction of the small interstitial proteoglycans biglycan, decorin and fibromodulin with transforming growth factor β. Biochem J. 1994; 302:527–534. [PubMed: 8093006]

435. Kolb M, Margets PJ, Sime PJ, Gauldie J. Proteoblycans decorin and biglycan differentially modulate TGF-β-mediated fibrotic responses in the lung. Am J Physiol Lung Cell Mol Physiol. 2001; 280:L1327–L1334. [PubMed: 11350814]

436. Bianco P, Fisher LW, Young MF, Termine JD, Robey PG. Expression and localization of the two small proteoglycans biglycan and decorin in developing human skeletal and non-skeletal tissues. J Histochem Cytochem. 1990; 38:1549–1563. [PubMed: 2212616]

437. Xu T, Bianco P, Fisher LW, Longenecker G, Smith E, Goldstein S, et al. Targeted disruption of the biglycan gene leads to an osteoporosis-like phenotype in mice. Nat Genet. 1998; 20:78–82. [PubMed: 9731537]
438. Chen X-D, Allen MR, Bloomfield S, Xu T, Young M. Biglycan-deficient mice have delayed osteogenesis after marrow ablation. Calcif Tissue Int. 2003; 72:577–582. [PubMed: 12724831]

439. Corsi A, Xu T, Chen X-D, Boyd A, Liang J, Mankani M, et al. Phenotypic effects of biglycan deficiency are linked to collagen fibril abnormalities, are synergized by decorin deficiency, and mimic Ehlers–Danlos-like changes in bone and other connective tissues. J Bone Miner Res. 2002; 17:1180–1189. [PubMed: 12102052]

440. Chen X-D, Fisher LW, Robey PG, Young MF. The small leucine-rich proteoglycan biglycan modulates BMP-4-induced osteoblast differentiation. FASEB J. 2004; 18:948–958. [PubMed: 15173106]

441. Moreno M, Muñoz R, Aroca F, Labarca M, Brandon E, Larraín J. Biglycan is a new extracellular component of the chordin-BMP4 signaling pathway. EMBO J. 2005; 24:1397–1405. [PubMed: 15775969]

442. Berendsen AD, Fisher LW, Kilts TM, Owens RT, Robey PG, Gutkind JS, et al. Modulation of canonical Wnt signaling by the extracellular matrix component biglycan. Proc Natl Acad Sci U S A. 2011; 108:17022–17027. [PubMed: 21969569]

443. Berendsen AD, Pinnow EL, Maeda A, Brown AC, McCartney-Francis N, Kram V, et al. Biglycan modulates angiogenesis and bone formation during fracture healing. Matrix Biol. 2014; 35:223–231. [PubMed: 24373744]

444. Weber CK, Sommer G, Michl P, Fensterer H, Weimer M, Gansauge F, et al. Biglycan is overexpressed in pancreatic cancer and induces G1-arrest in pancreatic cancer cell lines. Gastroenterology. 2001; 121:657–667. [PubMed: 11522750]

445. Melchior-Becker A, Dai G, Ding Z, Schafer L, Schrader J, Young MF, et al. Deficiency of biglycan causes cardiac fibroblasts to differentiate into a myofibroblast phenotype. J Biol Chem. 2011; 286:17365–17375. [PubMed: 21454527]

446. Schafer L, Babelova A, Kiss E, Hausser H-J, Baliova M, Krzyzankova M, et al. The matrix component biglycan is proinflammatory and signals through toll-like receptors 4 and 2 in macrophages. J Clin Invest. 2005; 115:2223–2233. [PubMed: 16025156]

447. Babelova A, Moreth K, Tsalastra-Greul W, Zeng-Brouwers J, Eickelberg O, Young MF, et al. Biglycan, a danger signal that activates the NLRP3 inflammasome via Toll-like and P2X receptors. J Biol Chem. 2009; 284:24035–24048. [PubMed: 19605353]

448. Moreth K, Frey H, Hubo M, Zeng-Brouwers J, Nastase MV, Hsieh LT, et al. Biglycan-triggered TLR-2- and TLR-4-signaling exacerbates the pathophysiology of ischemic acute kidney injury. Matrix Biol. 2014; 35:143–151. [PubMed: 24480070]

449. Zeng-Brouwers J, Beckmann J, Nastase MV, Iozzo RV, Schafer L, De novo expression of circulating biglycan evokes an innate inflammatory tissue response via MyD88/TRIF pathways. Matrix Biol. 2014; 35:132–142. [PubMed: 24361484]

450. Moreth K, Iozzo RV, Schafer L. Small leucine-rich proteoglycans orchestrate receptor crosstalk during inflammation. Cell Cycle. 2012; 11:2084–2091. [PubMed: 22580469]

451. Hsieh LT, Nastase MV, Zeng-Brouwers J, Iozzo RV, Schaefer L. Soluble biglycan as a biomarker of inflammatory renal diseases. Int J Biochem Cell Biol. 2014; 54C:223–235. [PubMed: 25091702]

452. Frey T, Schroeder N, Manon-Jensen T, Iozzo RV, Schaefer L. Biological interplay between proteoglycans and their innate immune receptors in inflammation. FEBS J. 2013; 280:2165–2179. [PubMed: 23350913]

453. Lorenzo P, Aspberg A, Önnerfjord P, Bayliss MT, Neame P, Heinegård D. Identification and characterization of asporin. A novel member of the leucine-rich repeat protein family closely related to decorin and biglycan. J Biol Chem. 2001; 276:12201–12211. [PubMed: 11152692]

454. Henry SP, Takanosu M, Boyd TC, Mayne PM, Eberspaecher H, Zhou W, et al. Expression pattern and gene characterization of asporin. A newly discovered member of the leucine-rich repeat protein family. J Biol Chem. 2001; 276:12212–12221. [PubMed: 11152695]

455. Kalamański S, Aspberg A, Lindblom K, Heinegård D, Oldberg Å. Asporin competes with decorin for collagen binding, binds calcium and promotes osteoblast collagen mineralization. Biochem J. 2009; 423:53–59. [PubMed: 19589127]
456. Kou I, Nakajima M, Ikegawa S. Expression and regulation of the osteoarthritis-associated protein asporin. J Biol Chem. 2007; 282:32193–32199. [PubMed: 17804408]

457. Nakajima M, Kizawa H, Saitoh M, Kou I, Miyazono K, Ikegawa S. Mechanisms for asporin function and regulation in articular cartilage. J Biol Chem. 2007; 282:32185–32192. [PubMed: 17827158]

458. Kizawa H, Kou I, Iida A, Sudo A, Miyamoto Y, Fukuda A, et al. An aspartic acid repeat polymorphism in asporin inhibits chondrogenesis and increases susceptibility to osteoarthritis. Nat Genet. 2005; 37:138–144. [PubMed: 15640800]

459. Gruber HE, Ingram JA, Hoelscher GL, Zinchenko N, Hanley EN Jr, Sun Y. Asporin, a susceptibility gene in osteoarthritis, is expressed at higher levels in the more degenerate human intervertebral disc. Arthritis Res Ther. 2009; 11:R47. [PubMed: 19327154]

460. Satoyoshi R, Kuriyama S, Aiba N, Yoshiro M, Tanaka M. Asporin activates coordinated invasion of scirrhous gastric cancer and cancer-associated fibroblasts. Oncogene. 2014; 29:650–660. [PubMed: 24441039]

461. Nishiu J, Tanaka T, Nakamura Y. Identification of a novel gene (ECM2) encoding a putative extracellular matrix protein expressed predominantly in adipose and female-specific tissues and its chromosomal localization to 9q22.3. Genomics. 1998; 52:378–381. [PubMed: 9790758]

462. Weyers A, Yang B, Solakylidirim K, Yee V, Li L, Zhang F, et al. Isolation of bovine corneal keratan sulfate and its growth factor and morphogen binding. FEBS J. 2013; 280:2285–2293. [PubMed: 23402351]

463. Ho LT, Harris AM, Tanioka H, Yagi N, Kinoshita S, Caterson B, et al. A comparison of glycosaminoglycan distributions, keratan sulphate sulphation patterns and collagen fibril architecture from central to peripheral regions of the bovine cornea. Matrix Biol. 2014; 38:59–68. [PubMed: 25019467]

464. Heinegård D, Larsson T, Sommarin Y, Franzén A, Paulsson M, Hedbom E. Two novel matrix proteins isolated from articular cartilage show wide distributions among tissues. J Biol Chem. 1986; 261:13866–13872. [PubMed: 3759994]

465. Oldberg Å, Antonsson P, Lindblom K, Heinegård D. A collagen-binding 59-kd protein (fibromodulin) is structurally related to the small interstitial proteoglycans PG-S1 and PG-S2 (decorin). EMBO J. 1989; 8:2601–2604. [PubMed: 2531085]

466. Hedbom E, Heinegård D. Interaction of a 59-kDa connective tissue matrix protein with collagen I and collagen II. J Biol Chem. 1989; 264:6898–6905. [PubMed: 2496122]

467. Heathfield TF, Onnerfjord P, Dahlberg L, Heinegard D. Cleavage of fibromodulin in cartilage explants involves removal of the N-terminal tyrosine sulfate-rich region by proteolysis at a site that is sensitive to matrix metalloproteinase-13. J Biol Chem. 2004; 279:6286–6295. [PubMed: 14660626]

468. Tillgren V, Onnerfjord P, Haglund L, Heinegard D. The tyrosine sulfate-rich domains of the LRR proteins fibromodulin and osteoadherin bind motifs of basic clusters in a variety of heparin-binding proteins, including bioactive factors. J Biol Chem. 2009; 284:28543–28553. [PubMed: 19700767]

469. Lauder RM, Huckerby TN, Nieduszynski IA. Structure of the keratan sulphate chains attached to fibromodulin isolated from bovine tracheal cartilage. Oligosaccharides generated by keratanase digestion. Biochem J. 1994; 302:417–423. [PubMed: 8092992]

470. Lauder RM, Huckerby TN, Nieduszynski IA. Lectin affinity chromatography of articular cartilage fibromodulin: Some molecules have keratan sulphate chains exclusively capped by alpha(2–3)-linked stialic acid. Glycoconj J. 2011; 28:453–461. [PubMed: 21892771]

471. Zhang Z, Krimmel J, Zhang Z, Hu Z, Seth P. Systemic delivery of a novel liver-detargeted oncolytic adenovirus causes reduced liver toxicity but maintains the antitumor response in a breast cancer bone metastasis model. Hum Gene Ther. 2011; 22:1137–1142. [PubMed: 21480822]

472. Svensson L, Narlid I, Oldberg A. Fibromodulin and lumican bind to the same region on collagen type I fibrils. FEBS Lett. 2000; 470:178–182. [PubMed: 10734230]

473. Hedbom E, Heinegård D. Binding of fibromodulin and decorin to separate sites on fibrillar collagen. J Biol Chem. 1993; 268:27307–27312. [PubMed: 8262971]
474. Kalamajski S, Oldberg Å. Fibromodulin binds collagen type I via Glu-353 and Lys-355 in leucine-rich repeat 11. J Biol Chem. 2007; 282:26740–26745. [PubMed: 17623650]

475. Kalamajski S, Oldberg Å. Homologous sequence in lumican and fibromodulin leucine-rich repeat 5–7 competes for collagen binding. J Biol Chem. 2009; 284:534–539. [PubMed: 19008226]

476. Ezura Y, Chakravarti S, Oldberg Å, Chervoneva I, Birk DE. Differential expression of lumican and fibromodulin regulate collagen fibrillogenesis in developing mouse tendons. J Cell Biol. 2000; 151:779–787. [PubMed: 11076963]

477. Krumdieck R, Höök M, Rosenberg LC, Volanakis JE. The proteoglycan decorin binds C1q and inhibits the activity of the C1 complex. J Immunol. 1992; 149:3695–3701. [PubMed: 1431141]

478. Sjoberg A, Onnerfjord P, Morgan M, Heinegard D, Blom AM. The extracellular matrix and inflammation: fibromodulin activates the classical pathway of complement by directly binding C1q. J Biol Chem. 2005; 280:32301–32308. [PubMed: 16046396]

479. Ameye L, Young MF. Mice deficient in small leucine-rich proteoglycans: novel in vivo models for osteoporosis, osteoarthritis, Ehlers–Danlos syndrome, muscular dystrophy, and corneal diseases. Glycobiology. 2002; 12:107R–116R.

480. Chakravarti S. Functions of lumican and fibromodulin: lessons from knockout mice. Glycoconj J. 2003; 19:287–293. [PubMed: 12975607]

481. Svensson L, Aszödi A, Reinholt FP, Fässler R, Heinegård D, Oldberg Å. Fibromodulin-null mice have abnormal collagen fibrils, tissue organization and altered lumican deposition in tendon. J Biol Chem. 1999; 274:9636–9647. [PubMed: 10092650]

482. Goldberg M, Septier D, Oldberg Å, Young MF, Ameye LG. Fibromodulin-deficient mice display impaired collagen fibrillogenesis in predentin as well as altered dentin mineralization and enamel formation. J Histochem Cytochem. 2006; 54:525–537. [PubMed: 16344330]

483. Goldberg M, Ono M, Septier D, Bonnefoix M, Kilts TM, Bi Y, et al. Fibromodulin-deficient mice reveal dual functions for fibromodulin in regulating dental tissue and alveolar bone formation. Cells Tissues Organs. 2009; 189:198–202. [PubMed: 18698127]

484. Goldberg M, Marchadier A, Vidal C, Harichane Y, Kamoun-Goldrat A, Kellermann O, et al. Differential effects of fibromodulin deficiency on mouse mandibular bones and teeth: a micro-CT time course study. Cells Tissues Organs. 2011; 194:205–210. [PubMed: 21597266]

485. Jepsen KE, Wu F, Peragallo JH, Paul J, Roberts L, Ezura Y, et al. A syndrome of joint laxity and impaired tendon integrity in lumican- and fibromodulin-deficient mice. J Biol Chem. 2002; 277:35532–35540. [PubMed: 12089156]

486. Chakravarti S, Paul J, Roberts L, Chervoneva I, Oldberg Å, Birk DE. Ocular and scleral alterations in gene-targeted lumican-fibromodulin double-null mice. Invest Ophthalmol Vis Sci. 2003; 44:2422–2432. [PubMed: 12766039]

487. Ameye L, Aria D, Jepsen K, Oldberg A, Xu T, Young MF. Abnormal collagen fibrils in tendons of biglycan/fibromodulin-deficient mice lead to gait impairment, ectopic ossification, and osteoarthritis. FAOSEB J. 2002; 16:673–680. [PubMed: 11978731]

488. Embree MC, Kilts TM, Ono M, Inkson CA, Seyed-Picard F, Karsdal MA, et al. Biglycan and fibromodulin have essential roles in regulating chondrogenesis and extracellular matrix turnover in temporomandibular joint osteoarthritis. Am J Pathol. 2010; 176:812–826. [PubMed: 20035055]

489. Grafe I, Yang T, Alexander S, Homan EP, Lietman C, Jiang MM, et al. Excessive transforming growth factor-beta signaling is a common mechanism in osteogenesis imperfecta. Nat Med. 2014; 20:670–675. [PubMed: 24793237]

490. Odorioso T, Di SM, Orecchia A, Di ZG, Piccinni E, Cianfarani F, et al. Monozygotic twins discordant for recessive dystrophic epidermolysis bullosa phenotype highlight the role of TGF-beta signalling in modifying disease severity. Hum Mol Genet. 2014; 23:3907–3922. [PubMed: 24599399]

491. Oldberg Å, Kalamajski S, Salnikov AV, Stuhr L, Mörgerlin M, Reed RK, et al. Collagen-binding proteoglycan fibromodulin can determine stroma matrix structure and fluid balance in experimental carcinoma. Proc Natl Acad Sci U S A. 2007; 104:13966–13971. [PubMed: 17715296]
492. Jian J, Zheng Z, Zhang K, Rackoehn TM, Hsu C, Levin A, et al. Fibromodulin promoted in vitro and in vivo angiogenesis. Biochem Biophys Res Commun. 2013; 436:530–535. [PubMed: 23770359]

493. Adini I, Ghosh K, Adini A, Chi ZL, Yoshimura T, Benny O, et al. Melanocyte-secreted fibromodulin promotes an angiogenic microenvironment. J Clin Invest. 2014; 124:425–436. [PubMed: 24355922]

494. Adini I, Adini A, Bazinet L, Watnick RS, Bielenberg DR, D’Amato RJ. Melanocyte pigmentation inversely correlates with MCP-1 production and angiogenesis-inducing potential. FASEB J. 2014; 29:662–670. [PubMed: 25406462]

495. Blochberger TC, Vergnes J-P, Hempel J, Hassell JR. cDNA to chick lumican (corneal keratan sulfate proteoglycan) reveals homology to the small interstitial proteoglycan gene family and expression in muscle and intestine. J Biol Chem. 1992; 267:347–352. [PubMed: 1370446]

496. Chakravarti S, Stallings RL, Sundarraj N, Cornuet PK, Hassell JR. Primary structure of human lumican (keratan sulfate proteoglycan) and localization of the gene (LUM) to chromosome 12q21.3–q22. Genomics. 1995; 27:481–488. [PubMed: 7558030]

497. Amjadi S, Mai K, McCluskey P, Wakefield D. The role of lumican in ocular disease. ISRN Ophthalmol. 2013; 2013:632302. [PubMed: 24558602]

498. Chakravarti S, Magnuson T, Lass JH, Jepsen KJ, LaMantia C, Carroll H. Lumican regulates collagen fibril assembly: skin fragility and corneal opacity in the absence of lumican. J Cell Biol. 1998; 141:1277–1286. [PubMed: 9606218]

499. Chakravarti S, Zhang G, Chervoneva I, Roberts L, Birk DE. Collagen fibril assembly during postnatal development and dysfunctional regulation in the lumican-deficient murine cornea. Dev Dyn. 2006; 235:2493–2506. [PubMed: 16786597]

500. Meij JTA, Carlson EC, Wang L, Liu C-Y, Jester JV, Birk DE, et al. Targeted expression of a lumican transgene rescues corneal deficiencies in lumican-null mice. Mol Vis. 2007; 13:2012–2018. [PubMed: 17982425]

501. Yeh L-K, Liu C-Y, Kao WWY, Huang C-J, Hu F-R, Chien CL, et al. Knockdown of zebrafish lumican gene (zlwum) causes scleral thinning and increased size of scleral coats. J Biol Chem. 2010; 285:28141–28155. [PubMed: 20551313]

502. Mienaltowski MJ, Birk DE. Mouse models in tendon and ligament research. Adv Exp Med Biol. 2014; 802:201–230. [PubMed: 24443029]

503. Nikitovic D, Papoutsidakis A, Karamanos N, Tzanakakis GN. Lumican affects tumor cell functions, tumor–ECM interactions, angiogenesis and inflammatory response. Matrix Biol. 2014; 35:206–214. [PubMed: 24060754]

504. Yoshioka N, Inoue H, Nakamishi K, Oka K, Yutsudo M, Yamashita A, et al. Isolation of transformation suppressor genes by cDNA subtraction: lumican suppresses transformation induced by v-src and v-K-ras. J Virol. 2000; 74:1008–1013. [PubMed: 10623765]

505. Leygue E, Snell L, Dotzlaw H, Hole K, Hiller-Hitchcock T, Roughley PJ, et al. Expression of lumican in human breast carcinoma. Cancer Res. 1999; 59:1348–1352. [PubMed: 9537227]

506. Leygue E, Snell L, Dotzlaw H, Troup S, Hiller-Hitchcock T, Murphy LC, et al. Lumican and decorin are differentially expressed in human breast carcinoma. J Pathol. 2000; 192:313–320. [PubMed: 11054714]

507. Sifaki M, Assouti M, Nikitovic D, Krasagakis K, Karamanos NK, Tzanakakis GN. Lumican, a small leucine-rich proteoglycan substituted with keratan sulfate chains is expressed and secreted by human melanoma cells and not normal melanocytes. IUBMB Life. 2008; 58:606–610. [PubMed: 17050378]

508. Brézillon S, Venteo L, Ramont L, D’Onofrio M-F, Perreau C, Pluot M, et al. Expression of lumican, a small leucine-rich proteoglycan with antitumour activity, in human malignant melanoma. Clin Exp Dermatol. 2007; 32:405–416. [PubMed: 17490399]

509. Vuillermoz B, Khoruzhenko A, D’Onofrio MF, Ramont L, Venteo L, Perreau C, et al. The small leucine-rich proteoglycan lumican inhibits melanoma progression. Exp Cell Res. 2004; 296:294–306. [PubMed: 15149859]
510. Brézillon S, Zeltz C, Schneider L, Terryn C, Vuillermoz B, Ramont L, et al. Lumican Inhibits B16F1 melanoma cell lung metastasis. J Physiol Pharmacol. 2009; 60(Suppl. 4):15–22. [PubMed: 20083847]

511. D’Onofrio M-F, Brézillon S, Baranek T, Perreau C, Roughley P, Maquart F-X, et al. Identification of β1 integrin as mediator of melanoma cell adhesion to lumican. Biochem Biophys Res Commun. 2008; 365:266–272. [PubMed: 17981144]

512. Brézillon S, Radwanska A, Zeltz C, Malkowski A, Ploton D, Bobichon H, et al. Lumican core protein inhibits melanoma cell migration via alterations of focal adhesion complexes. Cancer Lett. 2009; 283:92–100. [PubMed: 19394140]

513. Zeltz C, Brézillon S, Perreau C, Ramont L, Maquart F-X, Wegrowski Y. Lumcorin: a leucine-rich repeat 9-derived peptide from human lumican inhibiting melanoma cell migration. FEBS Lett. 2009; 583:3027–3032. [PubMed: 19686741]

514. Coulson-Thomas VJ, Coulson-Thomas YM, Gesteira TF, de Paula CA Andrade, Carneiro CR, Ortiz V, et al. Lumican expression, localization and antitumor activity in prostate cancer. Exp Cell Res. 2013; 319:967–981. [PubMed: 23399832]

515. Li X, Truty MA, Kang Y, Chopin-Laly X, Zhang R, Roife D, et al. Extracellular lumican inhibits pancreatic cancer cell growth and is associated with prolonged survival after surgery. Clin Cancer Res. 2014; 20:6529–6540. [PubMed: 25336691]

516. Nikitovic D, Berdiaik A, Zafriopoulos A, Katonis P, Tsatsakis A, Karamanos N, et al. Lumican expression is positively correlated with the differentiation and negatively with the growth of human osteosarcoma cells. FEBS J. 2008; 275:350–361. [PubMed: 18093185]

517. Nikitovic D, Chalkiadaki G, Berdiaik A, Aggelidakis J, Katonis P, Karamanos NK, et al. Lumican regulates osteosarcoma cell adhesion by modulating TGFbeta2 activity. Int J Biochem Cell Biol. 2011; 43:928–935. [PubMed: 21421073]

518. Pietraszek K, Chatron-Colliet A, Brezillon S, Perreau C, Jakubiak-Augustyn A, Krotkiewski H, et al. Lumican: a new inhibitor of matrix metalloproteinase-14 activity. FEBS Lett. 2014; 588:4319–4324. [PubMed: 25304424]

519. Li Y, Aoki T, Mori Y, Ahmad M, Miyamori H, Takino T, et al. Cleavage of lumican by membrane-type matrix metalloprotease-1 abrogates this proteoglycan-mediated suppression of tumor cell colony formation in soft agar. Cancer Res. 2004; 64:7058–7064. [PubMed: 15466200]

520. Vij N, Roberts L, Joyce S, Chakravarti S. Lumican regulates corneal inflammatory responses by modulating Fas–Fas ligand signaling. Invest Ophthalmol Vis Sci. 2005; 46:88–95. [PubMed: 15623759]

521. Lee S, Bowrin K, Hamad AR, Chakravarti S. Extracellular matrix lumican deposited on the surface of neutrophils promotes migration by binding to β2 integrin. J Biol Chem. 2009; 284:23662–23669. [PubMed: 19531489]

522. Carlson EC, Lin M, Liu C-Y, Kao WY, Perez VL, Pearlman E. Keratocan and lumican regulate neutrophil infiltration and corneal clarity in lipopolysaccharide-induced keratitis by direct interaction with CXCL1. J Biol Chem. 2007; 282:33502–33509.

523. Hayashi Y, Call MK, Chikama T-I, Liu H, Carlson EC, Sun Y, et al. Lumican is required for neutrophil extravasation following corneal injury and wound healing. J Cell Sci. 2010; 123:2987–2995. [PubMed: 20699360]

524. Wu F, Vij N, Roberts L, Lopez-Briones S, Joyce S, Chakravarti S. A novel role of the lumican core protein in bacterial lipopolysaccharide-induced innate immune response. J Biol Chem. 2007; 282:26409–26417. [PubMed: 17616530]

525. Shao H, Lee S, Gae-Scott S, Nakata C, Chen S, Hamad AR, et al. Extracellular matrix lumican promotes bacterial phagocytosis, and Lum−/− mice show increased Pseudomonas aeruginosa lung infection severity. J Biol Chem. 2012; 287:35860–35872. [PubMed: 22865855]

526. Lohr K, Sardana H, Lee S, Wu F, Huso DL, Hamad AR, et al. Extracellular matrix protein lumican regulates inflammation in a mouse model of colitis. Inflamm Bowel Dis. 2012; 18:143–151. [PubMed: 21484968]

527. Yamanaka O, Yuan Y, Coulson-Thomas VJ, Gesteira TF, Call MK, Zhang Y, et al. Lumican binds ALK5 to promote epithelium wound healing. PLoS One. 2013; 8:e82730. [PubMed: 24367547]
528. Bengtsson E, Neame PJ, Heinegård D, Sommarin Y. The primary structure of a basic leucine-rich repeat protein, PRELP, found in connective tissues. J Biol Chem. 1995; 270:25639–25644. [PubMed: 7592739]

529. Bengtsson E, Mörgelin M, Sasaki T, Timpl R, Heinegård D, Aspberg A. The leucine-rich repeat protein PRELP binds perlecan and collagens and may function as a basement membrane anchor. J Biol Chem. 2002; 277:15061–15068. [PubMed: 11847210]

530. Rucci N, Rufo A, Alamanou M, Capulli M, Del Fattore A, Åhrman E, et al. The glycosaminoglycan-binding domain of PRELP acts as a cell-type-specific NF-κB inhibitor that impairs osteoclastogenesis. J Cell Biol. 2009; 187:869–883.

531. Rucci N, Capulli M, Ventura L, Angelucci A, Peruzzi B, Tillgren V, et al. Proline/arginine-rich end leucine-rich repeat protein N-terminus is a novel osteoclast antagonist that counteracts bone loss. J Bone Miner Res. 2013; 28:1912–1924. [PubMed: 23559035]

532. Chen R, Dawson DW, Pan S, Ottenhof NA, de Wilde RF, Wolfgang CL, et al. Proteins associated with pancreatic cancer survival in patients with resectable pancreatic ductal adenocarcinoma. Lab Invest. 2015; 95:43–55. [PubMed: 25347153]

533. Iuga C, Seicean A, Iancu C, Buiga R, Sappa PK, Volker U, et al. Proteomic identification of potential prognostic biomarkers in resectable pancreatic ductal adenocarcinoma. Proteomics. 2014; 14:945–955. [PubMed: 24459066]

534. Happonen KE, Fürst CM, Saxne T, Heinegård D, Blom AM. PRELP protein inhibits the formation of the complement membrane attack complex. J Biol Chem. 2012; 287:8092–8100. [PubMed: 22267731]

535. Birke MT, Lipo E, Adhi M, Birke K, Kumar-Singh R. AAV-mediated expression of human PRELP inhibits complement activation, choroidal neovascularization and deposition of membrane attack complex in mice. Gene Ther. 2014; 21:507–513. [PubMed: 24670995]

536. Corpuz LM, Funderburgh JL, Funderburgh ML, Bottomley GS, Prakash S, Conrad GW. Molecular cloning and tissue distribution of keratocan. Bovine corneal keratan sulfate proteoglycan 37A. J Biol Chem. 1996; 271:9759–9763. [PubMed: 8621655]

537. Liu CY, Shiraiishi A, Kao CW, Converse RL, Funderburgh JL, Corpuz LM, et al. The cloning of mouse keratocan cDNA and genomic DNA and the characterization of its expression during eye development. J Biol Chem. 1998; 273:22584–22588. [PubMed: 9712886]

538. Liu C-Y, Birk D, Hassell JR, Kane B, Kao W-Y. Keratocan-deficient mice display alterations in corneal structure. J Biol Chem. 2003; 278:21672–21677. [PubMed: 12665512]

539. Pellegata NS, Dieguez-Lucena JL, Joensuu T, Lau S, Montgomery KT, Krahe R, et al. Mutations in KERA, encoding keratocan, cause cornea plana. Nat Genet. 2000; 25:91–95. [PubMed: 10802664]

540. Liskova P, Hysi PG, Williams D, Ainsworth JR, Shah S, de la Chapelle A, et al. Study of p.N247S KERA mutation in a British family with cornea plana. Mol Vis. 2007; 13:1339–1347. [PubMed: 17679937]

541. Conrad AH, Conrad GW. The keratocan gene is expressed in both ocular and non-ocular tissues during early chick development. Matrix Biol. 2003; 22:323–337. [PubMed: 12935817]

542. Igwe JC, Gao Q, Kizivat T, Kao WW, Kalajzic I. Keratocan is expressed by osteoblasts and can modulate osteogenic differentiation. Connect Tissue Res. 2011; 52:401–407. [PubMed: 21405980]

543. Melrose J, Fuller ES, Roughley PJ, Smith MM, Kerr B, Hughes CE, et al. Fragmentation of decorin, biglycan, lumican and keratocan is elevated in degenerate human meniscus, knee and hip articular cartilages compared with age-matched macroscopically normal and control tissues. Arthritis Res Ther. 2008; 10:R79. [PubMed: 18620607]

544. Carlson EC, Sun Y, Auletta J, Kao WW-Y, Liu C-Y, Perez VL, et al. Regulation of corneal inflammation by neutrophil-dependent cleavage of keratan sulfate proteoglycans as a model for breakdown of the chemokine gradient. J Leukoc Biol. 2010; 88:517–522. [PubMed: 20495072]

545. Wendel M, Sommarin Y, Heinegård D. Bone matrix proteins: isolation and characterization of a novel cell-binding keratan sulfate proteoglycan (osteoadherin) from bovine bone. J Cell Biol. 1998; 141:839–847. [PubMed: 9566981]
546. Sommarin Y, Wendel M, Shen Z, Hellman U, Heinegård D. Osteoadherin, a cell-binding keratan sulfate proteoglycan in bone, belongs to the family of leucine-rich repeat proteins of the extracellular matrix. J Biol Chem. 1998; 273:16723–16729. [PubMed: 9642227]

547. Onnerfjord P, Heathfield TF, Heinegard D. Identification of tyrosine sulfation in extracellular leucine-rich repeat proteins using mass spectrometry. J Biol Chem. 2004; 279:26–33. [PubMed: 14551184]

548. Sugars RV, Olsson ML, Marchner S, Hultenby K, Wendel M. The glycosylation profile of osteoadherin alters during endochondral bone formation. Bone. 2013; 53:459–467. [PubMed: 2337037]

549. Nikdin H, Olsson ML, Hultenby K, Sugars RV. Osteoadherin accumulates in the predentin towards the mineralization front in the developing tooth. PLoS One. 2012; 7:e31525. [PubMed: 2235537]

550. Johnson J, Rosenberg L, Choi HU, Garza S, Höök M, Neame P. Characterization of epiphycan: a small proteoglycan with a leucine-rich repeat core protein. J Biol Chem. 1997; 272:18709–18717. [PubMed: 9228042]

551. Shinomura T, Kimata K. Proteoglycan-Lb, a small dermatan sulfate proteoglycan expressed in embryonic chick epiphyseal cartilage, is structurally related to osteoinductive factor. J Biol Chem. 1992; 267:1265–1270. [PubMed: 1730648]

552. Johnson J, Shinomura T, Eberspaecher H, Pinero G, Decrombrugghe B, Hook M. Expression and localization of PG-Lb/epiphycan during mouse development. Dev Dyn. 1999; 216:499–510. [PubMed: 10633869]

553. Naka S, Zhou W, Henry SP, Gendron CMSJB, Shinomura T, Johnson J, et al. Phenotypic characterization of epiphycan-deficient and epiphycan/biglycan double-deficient mice. Osteoarthritis Cartilage. 2010; 18:88–96. [PubMed: 19932218]

554. Brachvogel B, Zaucke F, Dave K, Norris EL, Sterrn J, Dayakl M, et al. Comparative proteomic analysis of normal and collagen IX null mouse cartilage reveals altered extracellular matrix composition and novel components of the collagen IX interactome. J Biol Chem. 2013; 288:13481–13492. [PubMed: 23530037]

555. Reardon AJ, Le GM, Briggs MD, McLeod D, Sheehan JK, Thornton DJ, et al. Identification in vitreous and molecular cloning of opticin, a novel member of the family of leucine-rich repeat proteins of the extracellular matrix. J Biol Chem. 2000; 275:2123–2129. [PubMed: 10636917]

556. Pan Y, Carbe C, Powers A, Zhang EE, Esco JD, Grobe K, et al. Bud specific N-sulfation of heparan sulfate regulates Shp2-dependent FGF signaling during lacrimal gland induction. Development. 2008; 135:301–310. [PubMed: 18077586]

557. Hobby P, Wyatt MK, Gan W, Bernstein S, Tomarev S, Slingsby C, et al. Cloning, modeling, and chromosomal localization for a small leucine-rich repeat proteoglycan (SLRP) family member expressed in human eye. Mol Vis. 2000; 6:72–78. [PubMed: 10837509]

558. Monfort J, Tardif G, Roughley P, Reboul P, Boileau C, Bishop PN, et al. Identification of opticin, a member of the small leucine-rich repeat proteoglycan family, in human articular tissues: a novel target for MMP-13 in osteoarthritis. Osteoarthritis Cartilage. 2008; 16:749–755. [PubMed: 18164633]

559. Kanan Y, Siefert JC, Kinter M, Al-Ubaidi MR. Complement factor H, vitronectin, and opticin are tyrosine-sulfated proteins of the retinal pigment epithelium. PLoS One. 2014; 9:e105409. [PubMed: 25136834]

560. Le Goff MM, Sutton MJ, Slevin M, Latif A, Humphries MJ, Bishop PN. Opticin exerts its anti-angiogenic activity by regulating extracellular matrix adhesiveness. J Biol Chem. 2012; 287:28027–28036. [PubMed: 22669977]

561. Senger DR, Claffey KP, Benes JE, Perruzzi CA, Sergiou AP, Detmar M. Angiogenesis promoted by vascular endothelial growth factor: regulation through α1β1 and α2β1 integrins. Proc Natl Acad Sci U S A. 1997; 94:13612–13617. [PubMed: 9391074]

562. Senger DR, Perruzzi CA, Streit M, Koteliyangsky VE, de Fougerolles AR, Detmar M. The α1β1 and α2β1 integrins provide critical support for vascular endothelial growth factor signaling, endothelial cell migration, and tumor angiogenesis. Am J Pathol. 2002; 160:195–204. [PubMed: 11786413]
563. Pozzi A, Moberg PE, Miles LA, Wagner S, Soloway P, Gardner HA. Elevated matrix metalloprotease and angiostatin levels in integrin α1 knockout mice cause reduced tumor vascularization. Proc Natl Acad Sci U S A. 2000; 97:2202–2207. [PubMed: 10681423]

564. Borza CM, Pozzi A. Discoidin domain receptors in disease. Matrix Biol. 2014; 34:185–192. [PubMed: 24361528]

565. Madisen L, Neubauer M, Plowman G, Rosen D, Segarini P, Dasch J, et al. Molecular cloning of a novel bone-forming compound: osteoinductive factor. DNA Cell Biol. 1990; 9:303–309. [PubMed: 2372374]

566. Funderburgh JL, Corpuz LM, Roth MR, Funderburgh ML, Tasheva ES, Conrad GW. Mimecan, the 25-kDa corneal keratan sulfate proteoglycan, is a product of the gene producing osteoglycin. J Biol Chem. 1997; 272:28089–28095. [PubMed: 9346963]

567. Ujita M, Shinomura T, Kimata K. Molecular cloning of the mouse osteoglycin-encoding gene. Gene. 1995; 158:237–240. [PubMed: 7607548]

568. Tasheva ES, Corpuz LM, Funderburgh JL, Conrad GW. Differential splicing and alternative polyadenylation generate multiple mimecan mRNA transcripts. J Biol Chem. 1997; 272:32551–32556. [PubMed: 9405469]

569. Tasheva ES, Koester A, Paulsen AQ, Garrett AS, Doyle DL, Davidson JJ, et al. Mimecan/osteoglycin-deficient mice have collagen fibril abnormalities. Mol Vis. 2002; 8:407–415. [PubMed: 12432342]

570. Ge G, Seo NS, Liang X, Hopkins DR, Hook M, Greenspan DS. Bone morphogenetic protein-1/tolloid-related metalloproteinasenses process osteoglycin and enhance its ability to regulate collagen fibrillogenesis. J Biol Chem. 2004; 279:41626–41633. [PubMed: 15292192]

571. Rienks M, Papageorgiou AP, Frangogiannis NG, Heymans S. Myocardial extracellular matrix: an ever-changing and diverse entity. Circ Res. 2014; 114:872–888. [PubMed: 24577967]

572. Petretto E, Sarwar R, Grieve I, Lu H, Kumaran MK, Muckett PJ, et al. Integrated genomic approaches implicate osteoglycin (Ogn) in the regulation of left ventricular mass. Nat Genet. 2008; 40:546–552. [PubMed: 18443592]

573. Van Aelst LN, Voss S, Carai P, van LR, Vanhoutte D, Sanders-van WS, et al. Osteoglycin prevents cardiac dilatation and dysfunction after myocardial infarction through infarct collagen strengthening. Circ Res. 2015; 116:425–436. [PubMed: 25520363]

574. Tanaka K, Matsumoto E, Higashimaki Y, Katagiri T, Sugimoto T, Seino S, et al. Role of osteoglycin in the linkage between muscle and bone. J Biol Chem. 2012; 287:11616–11628. [PubMed: 22351757]

575. Barascuk N, Vassiliadis E, Zheng Q, Wang Y, Wang W, Larsen L, et al. Levels of circulating MfMCM-151, a degradation product of mimecan, reflect pathological extracellular matrix remodeling in apolipoprotein E knockout mice. Biomark Insights. 2011; 6:97–106. [PubMed: 22084568]

576. Cheng JM, Akkerhuis KM, Meilhac O, Oemrawsingh RM, Garcia-Garcia HM, van Geuns RJ, et al. Circulating osteoglycin and NGAL/MMP9 complex concentrations predict 1-year major adverse cardiovascular events after coronary angiography. Arterioscler Thromb Vasc Biol. 2014; 34:1078–1084. [PubMed: 24651681]

577. Neame PJ, Sommarin Y, Boynton RE, Heinegård D. The structure of a 38-kDa leucine-rich protein (Chondroadherin) isolated from bovine cartilage. J Biol Chem. 1994; 269:21547–21554. [PubMed: 8063792]

578. Bech-Hansen NT, Naylor MJ, Maybaum TA, Sparkes RL, Koop B, Birch DG, et al. Mutations in VNYX, encoding the leucine-rich proteoglycan nyltoaplin, cause X-linked complete congenital stationary night blindness. Nat Genet. 2000; 26:319–323. [PubMed: 11062471]

579. Pusch CM, Zeitz C, Brandau O, Pesch K, Achatz H, Feil S, et al. The complete form of X-linked congenital stationary night blindness is caused by mutations in a gene encoding a leucine-rich repeat protein. Nat Genet. 2000; 26:324–327. [PubMed: 11062472]

580. Ohta K, Lupo G, Kuriyama S, Keynes R, Holt CE, Harris WA, et al. Tsukushi functions as an organizer inducer by inhibition of BMP activity in cooperation with chordin. Dev Cell. 2004; 7:347–358. [PubMed: 15363410]
581. Haglund L, Tillgren V, Addis L, Wenglen C, Recklies A, Heinegard D. Identification and characterization of the integrin alpha2beta1 binding motif in chondroadherin mediating cell attachment. J Biol Chem. 2011; 286:3925–3934. [PubMed: 21127050]

582. Haglund L, Tillgren V, Onnerfjord P, Heinegard D. The C-terminal peptide of chondroadherin modulates cellular activity by selectively binding to heparan sulfate chains. J Biol Chem. 2013; 288:995–1008. [PubMed: 23172228]

583. Kvist AJ, Nyström A, Hultenby K, Sasaki T, Talts JF, Aspberg A. The major basement membrane components localize to the chondrocyte pericellular matrix—a cartilage basement membrane equivalent? Matrix Biol. 2008; 27:22–33. [PubMed: 17825545]

584. Hessle L, Stordalen GA, Wenglen C, Petzold C, Tanner E, Brorson SH, et al. The skeletal phenotype of chondroadherin deficient mice. PLoS One. 2013; 8:e63080. [PubMed: 23755099]

585. Batista MA, Nia HT, Cox KA, Ortiz C, Grodzinsky AJ, et al. Nanomechanical phenotype of chondroadherin-null murine articular cartilage. Matrix Biol. 2014; 38:84–90. [PubMed: 24892719]

586. Nakamura M, Sanuki R, Yasuma TR, Onishi A, Nishiguchi KM, Koike C, et al. TRPM1 mutations are associated with the complete form of congenital stationary night blindness. Mol Vis. 2010; 16:425–437. [PubMed: 20300565]

587. Bojang P Jr, Gregg RG. Topological analysis of small leucine-rich repeat proteoglycan nyctalopin. PLoS One. 2012; 7:e33137. [PubMed: 22485138]

588. Pearring JN, Bojang P Jr, Shen Y, Koike C, Furukawa T, Navy S, et al. A role for nyctalopin, a small leucine-rich repeat protein, in localizing the TRP melastatin 1 channel to retinal depolarizing bipolar cell dendrites. J Neurosci. 2011; 31:10060–10066. [PubMed: 21734298]

589. Cao Y, Posokhova E, Martemyanov KA. TRPM1 forms complexes with nyctalopin in vivo and accumulates in postsynaptic compartment of ON-bipolar neurons in mGluR6-dependent manner. J Neurosci. 2011; 31:11521–11526. [PubMed: 21832182]

590. Ohta K, Kuriyama S, Okafuji T, Gejima R, Ohnuma S-I, Tanaka H. Tsukushi cooperates with VG1 to induce primitive streak and Hensen’s node formation in the chick embryo. Development. 2006; 133:3777–3786. [PubMed: 16943268]

591. Morris SA, Almeida AD, Tanaka H, Ohta K, Ohnuma S-I. Tsukushi modulates Xnr2, FGF and BMP signaling: regulation of Xenopus germ layer formation. PLoS One. 2007; e1004. [PubMed: 17925852]

592. Kuriyama S, Lupo G, Ohta K, Ohnuma SI, Harris WA, Tanaka H. Tsukushi controls extodermal patterning and neural crest specification in Xenopus by direct regulation of BMP4 and x-delta-1 activity. Development. 2005; 133:75–88. [PubMed: 16319115]

593. Ohta K, Ito A, Kuriyama S, Lupo G, Kosaka M, Ohnuma S-I, et al. Tsukushi functions as a Wnt signaling inhibitor by competing with Wnt2b for binding to transmembrane protein Frizzled4. Proc Natl Acad Sci U S A. 2011; 108:14962–14967. [PubMed: 21856951]

594. Niimori D, Kawano R, Felemban A, Niimori-Kita K, Tanaka H, Ihn H, et al. Tsukushi controls the hair cycle by regulating TGF-β1 signaling. Dev Biol. 2013; 372:81–87. [PubMed: 22995554]

595. Niimori D, Kawano R, Niimori-Kita K, Ihn H, Ohta K. Tsukushi is involved in the wound healing by regulating the expression of cytokines and growth factors. J Cell Commun Signal. 2014; 8:173–177. [PubMed: 25159578]

596. Yamamoto A, Uchiyama K, Nara T, Nishimura N, Hayasaka M, Hanaoka K, et al. Structural abnormalities of corpus callosum and cortical axonal tracts accompanied by decreased anxiety-like behavior and lowered sociability in spock3-mutant mice. Dev Neurosci. 2014; 36:381–395. [PubMed: 25138526]

597. Ito A, Shinmyo Y, Abe T, Oshima N, Tanaka H, Ohta K. Tsukushi is required for anterior commissure formation in mouse brain. Biochem Biophys Res Commun. 2010; 402:813–818. [PubMed: 21055390]

598. Hossain M, Ahmed G, Naser IB, Shinmyo Y, Ito A, Riyadh MA, et al. The combinatorial guidance activities of draxin and Tsukushi are essential for forebrain commissure formation. Dev Biol. 2013; 374:58–70. [PubMed: 23206892]
599. Ferdous Z, Wei VM, Iozzo RV, Höök M, Grande-Allen KJ. Decorin-transforming growth factor-β interaction regulates matrix organization and mechanical characteristics of three-dimensional collagen matrices. J Biol Chem. 2007; 282:35887–35898. [PubMed: 17942398]

600. Cabello-Verrugio C, Brandan E. A novel modulatory mechanism of transforming growth factor-β signaling through decorin and LRP-1. J Biol Chem. 2007; 282:18842–18850. [PubMed: 17485468]

601. Fetting JL, Guay JA, Karolak MJ, Iozzo RV, Adams DC, Maridas DE, et al. FOXD1 promotes nephron progenitor differentiation by repressing decorin in the embryonic kidney. Development. 2014; 141:17–27. [PubMed: 24284212]

602. Brandan E, Gutierrez J. Role of skeletal muscle proteoglycans during myogenesis. Matrix Biol. 2013; 32:289–297. [PubMed: 23583522]

603. Jing J, Wu XJ, Li YL, Cai SQ, Zheng M, Lu ZF. Expression of decorin throughout the murine hair follicle cycle: hair cycle dependence and anagen phase prolongation. Exp Dermatol. 2014; 23:486–491. [PubMed: 24816226]

604. Ross MD, Bruggeman LA, Hanss B, Sunamoto M, Marras D, Klotman ME, et al. Podocan, a novel small leucine-rich repeat protein expressed in the sclerotic glomerular lesion of experimental HIV-associated nephropathy. J Biol Chem. 2003; 278:33248–33255. [PubMed: 12796502]

605. Shimizu-Hirota R, Sasamura H, Kuroda M, Kobayashi E, Saruta T. Functional characterization of podocan, a member of a new class in the small leucine-rich repeat protein family. FEBS Lett. 2004; 563:69–74. [PubMed: 15063725]

606. Mochida Y, Kaku M, Yoshida K, Katafuchi M, Atsawasuwan P, Yamauchi M. Podocan-like protein: a novel small leucine-rich repeat matrix protein in bone. Biochem Biophys Res Commun. 2011; 410:333–338. [PubMed: 21672516]

607. Didangelos A, Yin X, Mandal K, Baumert M, Jahangiri M, Mayr M. Proteomics characterization of extracellular space components in the human aorta. Mol Cell Proteomics. 2010; 9:2048–2062. [PubMed: 20551380]

608. Hutter R, Huang L, Speidl WS, Giannarelli C, Trubin P, Bauriedel G, et al. Novel small leucine-rich repeat protein podocan is a negative regulator of migration and proliferation of smooth muscle cells, modulates neointima formation, and is expressed in human atheroma. Circulation. 2013; 128:2351–2363. [PubMed: 24043300]

609. Bonnet F, Perin JP, Maillet P, Jolles P, Alliel PM. Characterization of a human seminal plasma glycosaminoglycan-bearing polypeptide. Biochem J. 1992; 288(Pt 2):565–569. [PubMed: 1463459]

610. Alliel PM, Perin J-P, Jollès P, Bonnet F. Testican, a multidomain testicular proteoglycan resembling modulators of cell social behaviour. Eur J Biochem. 1993; 214:347–350. [PubMed: 8389704]

611. Hartmann U, Maurer P. Proteoglycans in the nervous system—the quest for functional roles in vivo. Matrix Biol. 2001; 20:23–35. [PubMed: 11246001]

612. Vannahme C, Schubel S, Herud M, Gosling S, Hulsmann H, Paulsson M, et al. Molecular cloning of testican-2: defining a novel calcium-binding proteoglycan family expressed in brain. J Neurochem. 1999; 73:12–20. [PubMed: 10386950]

613. Bradshaw AD. Diverse biological functions of the SPARC family of proteins. Int J Biochem Cell Biol. 2012; 44:480–488. [PubMed: 22249026]

614. Charbonnier F, Périn J-P, Mattei M-G, Camuzat A, Bonnet F, Gressin L, et al. Genomic organization of the human SPOCK gene and its chromosomal localization to 5q31. Genomics. 1998; 48:377–380. [PubMed: 9545645]

615. Kohfeldt E, Maurer P, Vannahme C, Timpl R. Properties of the extracellular calcium binding module of the proteoglycan testican. FEBS Lett. 1997; 414:557–561. [PubMed: 9323035]

616. Hartmann U, Hülsmann H, Seul J, Röll S, Midani H, Breloy I, et al. Testican-3: a brain-specific proteoglycan member of the BM-40/SPARC/osteonectin family. J Neurochem. 2013; 125:399–409. [PubMed: 23418755]
617. Bonnet F, Perin JP, Charbonnier F, Camuzat A, Roussel G, Nussbaum JL, et al. Structure and cellular distribution of mouse brain testican. Association with the postsynaptic area of hippocampus pyramidal cells. J Biol Chem. 1996; 271:4373–4380. [PubMed: 8626787]

618. Scharenberg MA, Pippenger BE, Sack R, Zingg D, Ferralli J, Schenk S, et al. TGF-beta-induced differentiation into myofibroblasts involves specific regulation of two MKL1 isoforms. J Cell Sci. 2014; 127:1079–1091. [PubMed: 24424023]

619. Schnepp A, Komp LP, Hulsmann H, Kroger S, Paulsson M, Hartmann U. Mouse testican-2. Expression, glycosylation, and effects on neurite outgrowth. J Biol Chem. 2005; 280:11274–11280. [PubMed: 15657052]

620. Dhamija R, Graham JM Jr, Smaoui N, Thorland E, Kirmani S. Novel de novo SPOCK1 mutation in a proband with developmental delay, microcephaly and agenesis of corpus callosum. Eur J Med Genet. 2014; 57:181–184. [PubMed: 24583203]
A comprehensive classification of proteoglycans. The four families are based on their cellular and subcellular location, homology at the protein and genomic levels and the presence of unique protein modules which are often shared by members of a given class. The key for the various modules is provided in the bottom panel. For additional details about structure and function, please consult the text.
Fig. 2.
Schematic representation of the cell surface proteoglycans, which comprise transmembrane type I (the N-terminus is outside of the plasma membrane) proteoglycans (four syndecans, CSPG4/NG2, betaglycan and phosphacan) and six GPI-anchored proteoglycans, glypicans 1–6. The type of GAG chain and the major protease sensitive sites are indicated. The key for the various modules is provided in the bottom panel.
Fig. 3.
Schematic representation of the pericellular proteoglycans, which comprise perlecan agrin, and collagens XVIII and XV. The collagenous (COL) and non-collagenous (NC) domains of collagen XVIII are numbered on the top and bottom of the lower schematics. For brevity only the structure of collagen XVIII is shown. The key for the various modules is provided in the bottom panel.
Fig. 4.
Schematic representation of the hyaluronan- and lectin-binding proteoglycans (hyalectans), which comprise aggregan, versican, neurocan and brevican. The full-length versican (V0) and the three splice variants lacking GAGα (V1), GAGβ (V2) or both GAGα and GAGβ (V3) are shown. A new variant, V4, containing a portion of GAGβ is not shown. A GPI-anchored form of brevican is also not shown in the graphic. The dotted circles specify the globular domains (G1–G3) shared by the other hyalectans. These modules are composed of ~100 amino acids and have a characteristic consensus sequence with four disulfide-bonded Cys residues. The key for the various modules is provided in top right panel.
Fig. 5.
Phylogenetic tree of the small leucine-rich proteoglycans (SLRPs) and crystal structure of porcine decorin and biglycan decorin. (A) Dendrogram of the five human SLRP classes, numbered and color-coded. Protein sequences were first aligned with CLUSTALW before an unrooted dendogram was generated by a neighbor joining method using GenomeNet. (B) Cartoon ribbon diagram of the crystal structure of monomeric bovine decorin rendered with Pymol v1.7 (PDB accession number 1XKU). Vertical arrows indicate β-strands, while coiled ribbons indicate α-helices. The leucine-rich repeats (LRRs) are numbered above the
The sequence (SYIRIADTNIT) involved in binding to collagen type I [306,307] is highlighted in yellow. The terminal LRR Cys capping motif, known as the ear repeat, is also indicated [299].
Fig. 6.
Schematic representation of the modular organization of testican/SPOCK family of brain-specific proteoglycans. The five domains in roman numerals from N- to C-terminus are indicated at the top, and their structural homology is indicated at the bottom. Domains I and V appear to be specific for this family, whereas the other domains are shared with other proteoglycan gene families (see Fig. 1). The C-terminal Domain V contains two attachment sites for heparan sulfate chains labeled by asterisks. SP, signal peptide.