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Focus on Molecules: Decorin

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1. Structure

Decorin (NM_133507) is a ubiquitous small extracellular proteoglycan. It is a composite molecule ~100kda in size with a protein core and attached GAGs. It was cloned from a human embryonic fibroblast line and named PG40 for its protein core, ~40Kda. It has been known as PG-S2, bone proteoglycans-II, small leucine-rich protein-1B, dermatan sulphate proteoglycan-II, but decorin (DCN) was adopted based on its association with collagen fibrils, i.e., it “decorated” fibrils. It is the prototype of an expanding family of small leucine-rich repeat proteoglycans (SLRPs). The SLRP family has 5 classes and decorin is in class I.

Human decorin has 359 amino acids. The initial 16 amino acid signal peptide directs the nascent protein to the rough endoplasmic reticulum and is cleaved co-translationally. The propeptide is composed of 14 amino acids and regulates the attachment of glycosaminoglycan chains (GAG) with deletion leading to shorter GAGs. The protein core has major regulatory roles with functional modulation by the attached GAGs. The protein core consists of tandem leucine-rich repeats (LRR) flanked by conserved Cys-rich domains. The N-terminal cap motif Cx3Cx6Cx6C is conserved in class I SLRPs, Cys residues in this cluster form a disulfide knot protecting the hydrophobic core of LRR1 and stabilizing the domain. Twelve LRRs comprise the major central domain and give decorin a curved solenoid fold with a parallel β -sheet on the inside. LRR-11 extends laterally from the main body near the C-terminus and is known as the “ear” repeat, a distinctive feature of SLRPs. One of its Cys residues forms a disulfide bond with another Cys residue in LRR 12. This “ear” repeat is thought to be involved in folding of LRR12, but also may contribute to ligand recognition. Decorin can be substituted with one or two chondroitin/dermatan sulfate GAGs, in mammals, a single chain is attached to a serine residue near the N-terminus. There are three N-linked oligosaccharides attachment sites in LRRs7,9,11. Glycosylation is thought to aid in folding and secretion of the protein (McEwan et al., 2006). The crystal structure of decorin suggested a dimerization through concave faces, however, in vivo evidence favors a monomeric form, but monomer/dimer transitions may be relevant (Figure 1).

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2. Function

Decorin has a high affinity binding site for collagen at LRRs 4–6 and a low affinity site at the C-terminus. Molecular modeling suggested that decorin may interact with multiple collagen molecules simultaneously. Decorin is involved in the regulation of collagen fibrillogenesis and the decorin-deficient mouse has fragile skin and dysregulation of lateral fibril growth. This regulatory role is largely independent of the GAG chains. Decorin binds fibrils at the “d” and “e” bands, with its GAGs extending into the interfibrillar space. Decorin also bridges type VI collagen filaments to fibrils. In addition, it interacts with collagen types XII and XIV through its GAG chains and mediates the interaction of tenascin with collagen. All of these interactions are possible in the corneal stroma. The molecular basis of corneal transparency is dependent upon regular packing of fibrils with uniform small diameters, organized in an orthogonal lattice. SLRPs have been implicated at all levels. Decorin- and biglycan-deficient mice have mild stromal phenotypes. Biglycan is a closely related class I SLRP that competes for the same fibril binding region as decorin, with decorin having the higher affinity. Decorin-deficient mice demonstrated a significant up-regulation of biglycan expression suggesting a functional compensation. When this compensation was prevented in a compound decorin/biglycan-deficient mouse a severe stromal phenotype resulted. The stroma contained abnormal fibrils with large heterogeneous diameters and irregular profiles with altered packing. This is indicative of abnormal regulation of lateral fibril growth. In vitro studies demonstrated that biglycan functionally compensates for the loss of decorin at higher concentrations. The data indicate that decorin is the dominant corneal class I SLRP and a major regulator of corneal fibrillogenesis (Zhang et al., 2009).

Decorin has multiple non-structural functions; it binds to growth factors, e.g., TGF- β , FGF-2, TNF- α , PDGF and IGF-I, and sequesters them in the ECM, or presents them to receptors. It also modulates the TGF- β signal pathway through the LRP1 receptor, inhibiting cell growth and increasing extracellular matrix deposition. Decorin interacts with tyrosine kinase receptors and influences cell proliferation. The LRR7 domain binds to EGFR and ErbB4, activates the MAPK pathway, induces the CDK inhibitor P21 and down-regulates the receptor via a caveolin-mediated pathways thus affecting cell growth. The N-terminal domain can bind IGF-IR, through a MAPK-independent pathway and inhibit apoptosis. Interaction of decorin with the IGF-IR/mTOR/P70 S6 kinase signaling pathway can increase fibrillin-1 synthesis. Decorin binds Met, suppress intracellular levels of β -catenin thus inhibiting cell migration and growth. Decorin binds fibronectin and thrombospondin modulating cell adhesion and migration. Also, decorin can modulates cell immunity via binding of C1q complement, scavenger receptor-A or surfactant-associated protein-D. These interactions are consistent with decorin's involvement in diverse pathological processes such as tumor growth and metastasis, angiogenesis, renal and pulmonary fibrosis, muscular dystrophy, wound healing and myocardial infarction (Schaefer and Iozzo, 2008).

Perioperative decorin application decreased conjunctival scarring and enhanced outcome in glaucoma filtration surgery. A corneal inflammation model demonstrated decorin's involvement in angiogenesis through the IGFI receptor and retarded angiogenesis was observed in decorin deficient mice. Abnormal deposition in the trabecular meshwork may alter aqueous humor drainage in open angle glaucoma.

3. Disease Involvement

Altered decorin expression with dysfunctional extracellular matrices is associated with diseases including; Duchenne muscular dystrophy, Marfan's syndrome and tumors. Abnormal glycosylation of decorin was reported in Ehlers-Danlos syndrome. In Lyme

disease, the spirochete *Borrelia burgdorferi*, attaches to the extracellular matrix using decorin binding adhesins.

Human congenital stromal corneal dystrophy is the only known disease associated with a mutant decorin gene. Two independent families were described, a single base pair deletion at either bp941 or bp967, both result in a frameshift mutation and a truncated protein core lacking the C-terminal 33 amino acids. Patients develop bilateral corneal opacities perinatally. The stroma has layers of relatively normal collagen fibrils separated by abnormal layers with thin, disorganized fibrils/filamentous material embedded in an electron-lucent ground substance (Bredrup et al., 2005). This disease is autosomal dominant, only heterozygous patients carrying a normal and mutant decorin allele were found, suggesting that homozygosity results in a lethal phenotype. The mutation affects the ear region and it is tempting to speculate that this alters ligand interactions resulting in the dysfunctional matrix. An involvement of dominant-negative interactions also is suggested.

4. Future Studies

Decorin is multifaceted functioning both as a structural molecule and matrikine. It can bind to ECM and sequesters cytokines and/or bind receptors or make cytokines available. These different interactions are likely to contribute tissue-specific function, however mechanisms underlying the differences remain to be elucidated

Mouse models mimicking human congenital corneal stromal dystrophy in *Dcn*^{+/-} and *-/-* backgrounds would provide opportunities to elucidate the structure/function relationship of corneal decorin. A phenotype has only been described in ocular tissues despite decorin being ubiquitous, suggesting a cornea-specific mechanism. SLRPs can be functionally redundant and an influence on expression of other SLRPs and matrix components should be considered as well as alterations of receptor binding and signaling. In addition, analysis of interactions among 6 SLRPs expressed in the cornea and the role(s) of these interactions in pathobiology is important.

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References

- Bredrup C, Knappskog PM, Majewski J, Rodahl E, Boman H. Congenital stromal dystrophy of the cornea caused by a mutation in the decorin gene. *Invest Ophthalmol Vis Sci*. 2005; 46:420–426. [PubMed: 15671264]
- 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]
- Schaefer 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]
- Zhang G, Chen S, Goldoni S, Calder BW, Simpson HC, Owens RT, McQuillan DJ, Young MF, Iozzo RV, Birk DE. 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]

Figure 1.

Structural features of decorin. (A) Domain structure of the decorin protein core. From N- to C-terminus: signal peptide (SP); propeptide (PP); the GAG attachment site at serine residue in the N-terminal Cys-rich domain; central LRR repeats; C-terminal Cys-rich domain. There are 3 N-linked oligosaccharide attachment sites in the LRR domains. Human congenital stromal dystrophy is caused by a mutant decorin gene resulting in a C-terminal truncated protein (TS, truncation site). (B) Swiss model (Automated mode) of a normal mouse decorin and a truncated decorin lacking the C-terminal 33 amino acids, LRR domains are numbered from N-terminus to C-terminus (1 to 12). N-terminal Cys residues form a disulfide knot between N-terminus and LRR1, one Cys residue in LRR11 forms a disulfide bond with a Cys residue in LRR12 at C-terminus (Cys residues are brown, disulfide bonds are orange). Red arrow indicates the region of C-terminal truncation involving a deletion of LRR12 and part of LRR11, i.e. "ear repeat".