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Structural Insights into Protein-Ligand Interactions of Small Leucine Rich Repeat Proteoglycans with a Large Number of Binding Partners: An Overview

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Abstract

Small leucine rich repeat proteoglycans (SLRPs) exist in the extracellular matrix. SLRPs contain tandem arrays of LRRs flanked by cysteine clusters at the both N- and C-termini. The extreme N- and/or C-termini contain low complexity sequences, glycosaminoglycan (GAG) chain and/or sulfated tyrosine residues in some members of SLRPs. The LRR solenoid structure may be divided into four parts consisting of a concave surface, an ascending surface, a convex surface, and a descending surface. SLRPs share many biological functions including co*llagen fibrillogenesis, signaling*, innate immunity, and inflammation through the binding of various ligands. We undertake a comprehensive literature search of publications in order to make a list of ligands of SLRPs. We describe and discuss the interacting sites of SLRPs to binding partners. The protein-ligand interactions occur on not only the concave surface but also the ascending surface and the N- or C-terminal capping regions. In addition, the extreme N- and/or C-terminal regions with the GAG chains or sulfated tyrosine residues participate in ligand-interactions.

Keywords: Small leucine rich repeat proteoglycan, Leucine rich repeat, Solenoid structure, Concave face, Ascending loop, Capping structure, Ligand interactions, Glycosamoninoglycan

Abbreviations: BAI: Brain-specific Angiogenesis Inhibitor; BMP: Bone Morphogenic Protein; CCP: Complement Control Protein; C4BP: C4b-Binding Protein; CpG: Cytosine – phosphate – Guanine; CpG-DNA; CpG Dideoxynucleotide motif; CS: Chondroitin Sulfate; CTGF/CCN: Connective Tissue Growth Factor; CXCL1: CXC chemokine KC; Dbp: Decorin-binding protein; DS: Dermatan Sulfate; ECM2: Extracellular Matrix 2; EGFR: Epidermal Growth Factor Receptor; FGF: Fibroblast Growth Factor; FHR: Complement factor H-related protein; GAG: Glycosaminoglycan; HS: Heparan Sulphate; Hsp47: Heat shock protein 47; Ig: Immunoglobulin-like domain; IR: Insulin Receptor; IGF: Insulin like Growth Factor; IGF1R: Insulin-like Growth Factor 1 Receptor; LDL: Low-Density Lipoprotein; LOX: Lysyl Oxidase; LPS: Lipopolysaccharide; LRP-1: Low-density lipoprotein Receptor-related Protein 1; LRR: Leucine Rich Repeat; MAGP-1: Microfibril-Associated Glycoprotein-1; MBL: Mannose-Binding Lectin; Met: Hepatocyte growth factor receptor; MMP: Matrix Metalloproteinase; MUSK: Muscle-Specific Kinase; NF-κB: Nuclear Factor-kappa B; p75NTR: Low-affinity nerve growth factor receptor; PDGF: Platelet-Derived Growth Factor; PSMD2: 26S Proteasome non-ATPase regulatory subunit 2; SLRP: Small Leucine Rich Repeat Proteoglycan; TGF: Transforming Growth Factor; TLR: Toll-Like Receptor; TNF-α: Tumor Necrosis Factor-alpha; TN-X: Tenascin X; TSP-1: Thrombospondin-1; TSR: TSP Type-1 repeat; VEGFR-2: Vesicular Endothelial Growth Factor Receptor 2; vWF: von Willebrand Factor; WISP-1: Wnt-I-induced Secreted Protein-1; TRPM1: Transient Receptor Potential Melastatin 1

Introduction

Small leucine rich repeat proteoglycans (SLRPs) exist in the extracellular matrix [1-7]. They are divided into five distinct classes; class I consists of biglycan, decorin asporin (PLAP-1), and ECM2, class II is fibromodulin, lumican, PRELP, keratocan, and osteomodulin/osteoadherin, class III is osteoglylcin/mimecan, epiphycan, and opticin, class IV is chondroadherin-like protein, nyctalopin, and Tsukushi, and class V is podocan and podocan-like protein 1 (**Table S1**) [8,9]. SLRPs contain tandem arrays of LRRs flanked by cysteine clusters at the both N- and C-termini [8,9]. The disulfide bonds of the Cys clusters stabilize a capping structure that shields the hydrophobic core of the first LRR unit at the N-terminus and the last unit at the C-terminus [10,11]. The extreme N- and/or C-termini contain low complexity sequences, glycosaminoglycan (GAG) chain and/or sulfated tyrosine residues in some members of SLRPs. The LRRs adopting short β-strands at positions 3 – 5 form a parallel β-sheet and form a solenoid structure of a super helix arrangement [10-12]. The LRR solenoid structure may be divided into four parts consisting of a concave face, an ascending face, a convex face, and a descending face (**Figure 1**) [10,13]. LRRs are characterized by a common molecular architecture adapted to protein–protein interactions [11]. SLRPs are capable of binding to various ligands through which play versatile functions including collagen fibrillogenesis, cellular proliferation, survival, adhesion, migration, differentiation, invasion, signaling, innate immunity and inflammation [5,6].

Many reviews on the functions, structures, ligands, and diseases of SLRPs [1-9] and individual members have been published; the individual members reviewed are decorin [14-19], biglycan [16,17,20,21], fibromodulin [22,23], lumican [24], osteoglycin [25,26], and Tsukushi [27,28]. Gubbiotti et al., [14] did a comprehensive analysis of decorin-binding partners and discussed their versatile functions; there is the STRING database that is a database of known and predicted protein-protein interactions [29].

Here we undertake a comprehensive literature search of publications in order to make a list of ligands of all members of SLRPs. We describe and discuss the interacting sites of SLRPs to the binding partners. The protein-ligand interactions occur on not only the concave face but also the ascending face and the N-terminal capping region. In addition, the extreme N- and/or C-terminal regions with the GAG chains or sulfated tyrosine residues participate in ligand-interactions.

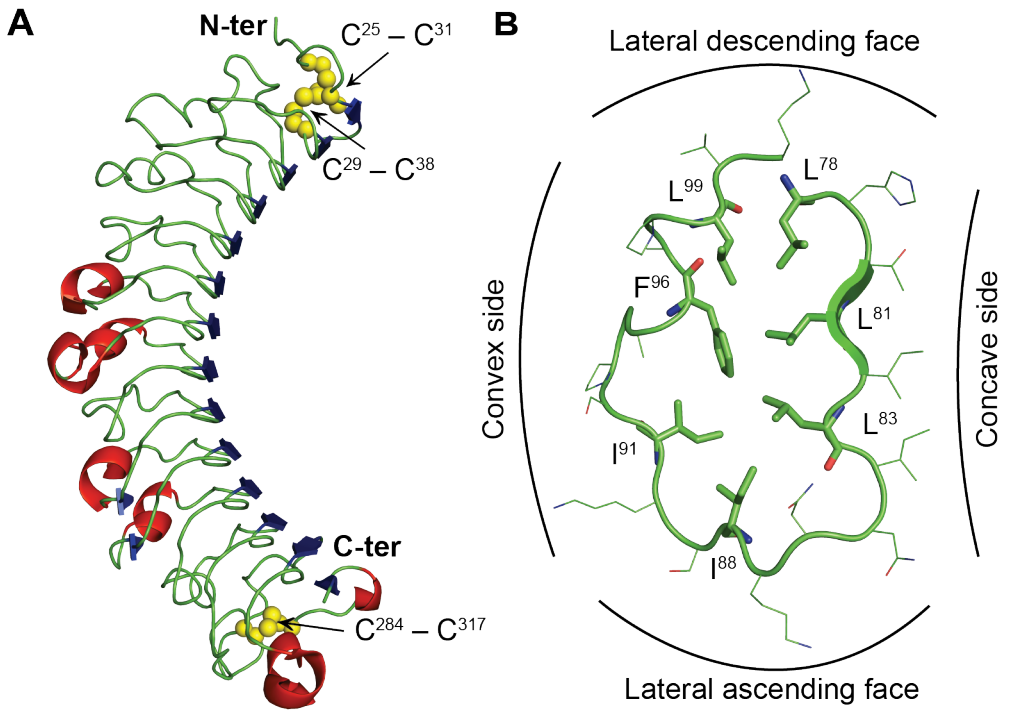

Figure 1. Structure of decorin (PDB ID: 1XKU). **(A)** Cartoon backbone representation and close-up view of decorin. Secondary structure elements and intramolecular disulfide bonds are depicted. **(B)** Cartoon backbone representation of a typical LRR fragment (LRR3) consisting of 78-LHTLILINNKI SKISPGAFAPLVK-101 in decorin. By convention, the loop fragments connecting the concave to the convex side of the repeats from the lateral ascending face, whereas the loops connecting the convex to the concave side form the lateral descending face.

Sequence Features and LRR Solenoid Structures of SLRPs

The repeat numbers of LRRs in SLRPs range from 8 to 22 (**Table S1**). Class I and II have 12 repeats; only ECM2 has 15 repeats [9]. The N-terminal residues of class II SLRPs and class I ECM2 form one additional strand of the concave β-sheet. The repeat number of class III, IV, and V are 8, 12, and 22 or 18, respectively; only nyctalopin has 13 repeats. Most SLRPs including decorin and biglycan at the extreme N-terminal side undergo glycosylation: glycosaminoglycan (GAG) including chondroitin sulfate (DS) and/or dermatan sulfate (CS) [7]. Fibromodulin, lumican, and osteomodulin also undergo sulphation in tyrosine clusters in the extreme N-terminal regions [30,31]. Some SLRPs show low complexity sequences flanking LRR domains on the extreme N-terminal sides [9]; they are poly-Asp in asporin and Arg/Pro-rich amino acids in PRELP. Biglycan and decorin form stable dimers through concave face interactions [32,33].

Crystal structures of five SLRPs are available (**Table S1**) [32-35]. The remaining SLRPs have been predicted by AlphaFold [36]. Histidines and aromatic residues are markedly concentrated on the concave faces of fibromodulin and chondroadherin [34]. Aromatic - aromatic and methionine – aromatic interactions frequently occur [9]. The HELFIT program calculates the helix parameters of helix axis, helix pitch (*P*), helix radius (*R*), number of repeats per turn (*N*), and handedness [37,38]. In LRRs, the Cα coordinates of the consensus leucine residue at position 4 (located in the center of short β-strands) in individual repeat units are used for the analysis. **Table S1** and **Figure S1** show the helix parameters. The LRR domains are well represented by right-handed helices. The helix parameters of class III remarkably differ from those of the other classes (I, II, IV, and V); class III shows the largest *P* and the smallest *R*.

A List of Ligands of SLRPs

Table 1 shows a list of ligands of SLRPs. Binding partners of ECM2 and podocan-like 1 protein are not identified; the predicted candidates are described in the STRING database [29]. We tentatively classified ligands into nine groups from the point of view of plausible binding sites of SLRPs to their ligands.

Table 1. A list of ligands of SLRPs.

Class	SLRPs	Ligands
I	Decorin	collagen I [40-43,51-53]; collagen II and III [44,53];
		collagen V [45,52]; collagen VI [46-48,51,55];
		collagen XII [49]; collagen XIV [50,54]; TGF-β [77,84];
		Met [15,95,96]; LRP1 [101-103]; dermatopontin [109,110];
		C1q [52,125]; MBL [129]; TLR2 and TLR4 [130];
		EGFR, ERbB2, and ErbB4 [15,149-151];
		IGF-1 [159]; IGF-2 and insulin [160]; IGF1R [159-163];
		fibronectin [167-169]; VEGFR-2 [170, 171]; HBHA [182];
		α2β1 integrin [184,185]; TN-X [194]; LDL [195,196]
		DbpA and DbpA [197-206]; vWF [208]; matrilin-1 [209];
		TNF-α [215]; TSP-1 [219,220]; PDGF [229,230]; Zn^{2+} [231];
		fibrinogen [232,233]; myostatin [236,237];
		CTGF/CCN2 [236-240]; WISP-1/CCN4 [241];
		apolipoprotein(a) [244]; MAGP-1 and fibrillin-1 [245];
		tropoelastin [246]; filamin-A [250]; Hsp47 [259]; resistin [257]
	Biglycan	collagen I [53,56]; collagen II [44,53]; collagen III [53,57];
		collagen VI [55]; collagen IX [58]; TGF-β [78,79]; BMP-2 [85,86];
		BMP-4 [90,210]; LRP6 [104,105]; collagen V and C1q [124];
		MBL [129]; C1q [126]; CD14 [133]; TLR2 and
		TLR4 [131,132,145], CpG DNA [136]; TLR3 [139];

		P2X4/P2X7 [146]; IGF1R [164]; TGF-β [154,155];
		DbpA and DbpB [207]; matrilin-1 [209]; chordin [210];
		α-dystroglycan [214]; TNF-α [215]; CD44 [222];
		FGF-2 [230]; α– and γ– sarcoglycan [238]; MAGP-1 [246];
		topoelastin [246]; MuSK [266]; endostatin [268]
	Asporin	collagen I [66]; Ca^{2+} [66]; TGF-β1 [80-83]; BMP2 [87,88];
		FGF-2 [106]; ErbB2 [152]; IGF1R [165]; PSMD2 [267];
		CD44 [223,224]; smad2/3 [254]
	ECM2	–
II	Fibromodulin	collagen XII [48]; collagen I [58-63]; collagen II [59,62];
		collagen VI [64]; LOX [74]; TGF-β [78,79]; FGF-2,
		TSP-1, the NC4 domain of collagen IX, and interleukin-10 [121];
		MMP-13 [121]; FH [127]; C1q [127]; Ty384 variant of FH [177];
		FHR1 and FHR5 [180]; C4BP [217]; the NC4 domain of collagen
		IX [218]; myostatin [234, 235]; Hsp47 [258]; fibronectin [112]
	Lumican	collagen I [64,67]; MMP14 [118-120]; LPS [134,136];
		caveolin 1 and CD14 [136], CpG DNA [136];
		β1, β2, αM, and αL and α2β1 integrins [186-189]; ALK5 [243];
		CXCL1 [253]; p120 [253,270]; tubulin [255,256];
		aggrecan [258]; Hsp47 [259]; Fas ligand [262]
	PRELP	IGF1R [166]; p75NTR [166]; FH [176]; FHR1 and FHR5 [180];
		p65 NF-κB [213]; C4BP [217]; perlecan and collagen [226];
		heparin and HS [227]
	Keratocan	collagen I [68]; CXCL1 [253]
	Osteomodulin	Collagen I [34]; BMP-2 [89]; PRELP, FGF-2, fibronectin, CILP,
		TSP-1, and antithrombin III [121]; FH [128]; C1q [128]
		FHR1 and FHR5 [180]; αvβ3 integrin [190]; C4BP [217];
		the NC4 domain of collagen IX [218]
III	Osteoglycin	collagen I [67]; BMPs [94]; VEGFR-2 [172,173]
	Opticin	collagen fibrils (including collagens II, and XI or V/XI) [71]
		heparin, HS, chondroitin 4-sulfate, and DS [228];
		collagen XVIII [228], retinal growth hormone [271]
	Epiphycan	collagens [72]
IV	Chondroadherin	collagen II [69]; α2β1 integrin [191,192]; C1q [128]; FH [128]
		C4BP [217]; HS [242]
	Nyctalopin	TRPM1 [273,274]; mGluR6 [274]
V	Tsukushi	TGF-β1 [83], CTGF/CCN2 [83]; BMP-4 [83,91-93];

		FGF-8, FGF-8b, FGF-10 [83,91,107]; nodal and Vg1 [83,115],
		netrin 1 [91]; Delta [83]; Sox2 [92]; chordin [93];
		Wnt2b and Frizzled4 [263]; Frizzled3 [264]
	Podocan	Wnt4 [265]
	Podocan-like protein 1	–

Binding Sites of SLRPs to Ligands

Concave face

Collagen: The collagen family comprises 28 members (I–XXVIII) in vertebrates [39]. Various types of collagens are bound to SLRPs [3]; decorin (I, II, III, V, VI, XII, XIV) [40-55], biglycan (I, II, III, VI) [44,53,55-58] and fibromodulin (I, II, VI) [49,59-65] (**Table 1**). Asporin [66], lumican [64,67], keratocan [68], osteomodulin/osteoadherin [35], osteoglycin/mimecan [68], and podocan [69] bind to collagen I, while chondroadherin binds to collagen II [70]. Epiphycan and opticin also bind collagens [71,72]. The binding sites have been investigated in decorin, asporin, fibromodulin, lumican, and osteomodluin [35,42,43,59,64,66,67,73,74]. These experimental results indicate that the collagen binding site is mapped on the concave face or the ascending loop [9,75,76]. Collagen triple helix may span across 7-8 LRRs in the SLRPs [9]. The binding is probably due to electrostatic interactions and/or aromatic/histidine − aromatic interactions [9,35,73]. In addition to polar, ionic, and cation-π interactions, hydrophobic interaction and CH/π interaction might contribute to the binding.

Transforming growth factor-β (TGF- β): TGF-β is synthesized as a latent form (L-TGF-β) containing a 25-kDa N-terminal latency-associated peptide (LAP) and a 12-kDa C-terminal growth factor (mTGF-β) domain. TGF-β exists in three isoforms (TGF-β1, TGF-β2, and TGF-β3) in humans. Decorin, biglycan, and fibromodulin bind to the three isoforms [77-79]. Fibromodulin interacts differently with different TGF-β ligands; fibromodulin dampens TGF-β3-mediated antimotility effects [79]. Asporin and Tsukusi also bind to TGF-β1 [80-83]. Decorin fragment Leu155-Val260 (LRR5 to LRR9) interacts with TGF-β [84]. Asporin amino acids 159-205 (LRR4 to LRR6) mediate its interaction with TGF-β1 [81].

Bone morphogenetic proteins (BMP-2 and BMP-4): BMP-2 and BMP-4 being 92% identical are also members of the TGF-β protein family. Biglycan, asporin, and osteomodulin interact with BMP-2 [85-89]. In biglycan LRR2 and LRR3 sit on a face interacting with BMP-2 [86]. The interacting site in asporin is LRR5 [88]. Osteomodulin binds to BMP-2 via LRR10 and LRR11 and also forms complexes with BMP receptors [89]. BMP-4 binding is coincident with biglycan [90]. Tsukusi interacts with BMP-4 [83,91,92]. Tsukushi binds directly to both BMP4 and chordin, and consequently forms a ternary complex with them [93]. Osteoglycin binds BMPs [94].

Hepatocyte growth factor receptor (Met): Decorin binds directly and with high affinity (K_d = ~1.5 nM) to Met [15,95,96]. The structure of the InB-Met complex is available [97-100]. An LRR protein, InlB, consists of an N-terminal LRR region, a central B repeat and three C-terminal GW domains; the LRR region is flanked N-terminally by a helical cap and C-terminally by an Ig-like inter-repeat region. The structure reveals that there are two contacts in the InlB-Met complex [99]. The concave face of the InlB LRR region interacts tightly with the first Ig domain of the Met stalk. A second contact is between InlB and the Met Sema. In the decorin-Met interaction, we strongly infer that the Met binding site is located on the concave face of the decorin LRR region.

Low density lipoprotein receptor-related proteins 1 and 6 (LRP1 and LRP6): LRP1 is an endocytic receptor for decorin [101-103]. Biglycan insteracts with LRP6 [104,105], which activates the receptor and attenuates β-catenin degradation [105]. The internal region of LRR6 in decorin is required for interaction with LRP-1 [102]. Thus, we infer that LRP1 interact with decorin through the concave surfce of the decorin LRR region.

Fibroblast growth factors (FGFs): Asporin directly interacts with FGF-2 [106]. Tsukushi also interacts with FGF-8, FGF-8b, and FGF-10 [83,91,107]. The direct binding to FGF-2 promotes FGF-2–FGF receptor 1 (FGFR1) complex formation. Awata et al., [106] reason that the interacting site of asporin is LRR5, while Kubo et al., [19] and Seidler et al., [108] suggest that FGF2 binds to the GAG chain of decorin.

Dermatopontin (Tyrosine-rich acidic matrix protein): Decorin interacts with dermatopontin [109,110]. The core protein of the decorin molecule binds to dermatopontin and the interaction is probably ionic [110]. The dermatopontin-decorin complex binds fold more TGF-β1 than did each component individually [111]. In Silico analysis predicts that the entire concave face of decorin interacts with dermatopontin [112].

Nodal and Vg1: Nodal and Vg1 contain TGF-β domains [113,114]. Chick Tsukushi binds to nodal and Vg1 [83,115]. The structures of two LRR proteins (GARP and LRRC33) in complex with TGF-β1 are available [116,117]. The two LRR proteins together contain 22 LRRs. Three main interfaces occur; namely GARP: mTGF- $\beta1_B$, GARP: LAP_A, and GARP: LAP_B. The binding footprint of TGF- β1 to GARP comprises not convex

face but lateral ascending and concave faces (LRR4 to LRR11) [116]. All of myostatin, BMP-2, BMP-4, nodal, and Vg1 contain the N-terminal region corresponding to the latent peptide (L-TGF-β) of TGF-β and the C-terminal mTGF-β. Thus, we infer that these TGF family proteins interact with both lateral ascending and concave faces of the SLRPs (decorin, biglycan, fibromodulin, asporin, osteomodulin, and Tsukushi).

Matrix metalloproteinase-14 (MMP-14) and -13 (MMP-13): Lumican interacts with MMP-14 [118-120] and fibromodulin with MMP-13 [121]. The interactions of lumican-derived peptides and MMP-14 were investigated [122]; lumicorin and L9M of the peptide sequences are SSLVELDLSYNKLKNIP (LRR10) and ELDLSYNKLK, respectively [122]. An in silico approach predicted that decorin, biglycan, fibromodulin, and lumican bind to MMP-14 through their concave face [123].

Netrin-1: Netrin-1 as well as NetrinG1 is a member of the EGF family. It contains an Nterminal laminin domain, three EGFlike domains and a C-terminal cell interaction netrin-like domain. Tsukushi interacts with netrin-1 [91]. The structures of NetrinG1 – NGL1 and NetrinG2 – NGL2 complexes have been determined [124]. NGLs are an LRR protein and contains nine LRRs forming the LRR domain. Three loops of the N-terminal laminin domain of NetrinG1 and NetrinG2 contact the concave faces of the LRR domains of NGL and NGL2, respectively. We infer that the concave face of the Tsukusi LRR domain is included in the interaction with netrin-1 via its three corresponding loops.

C1q and Mannose-binding lectin (MBL): C1q and mannose binding lectin (MBL), a member of the collectin family of proteins, have a characteristic triple-helical collagen-like region (CLR) at the N terminus. Decorin [52,125], biglycan [126]; fibromodulin [127], osteomodulin [128], and chondroadherin [128] bind to C1q, while decorin and biglycan efficiently bind to MBL [129]. C1q but not FH directly interacts with the 10-kDa N-terminal fragment of fibromodulin [127]. Decorin and fibromodulin bind the N-terminal collagenous part of complement C1q [125,127]. Taken together, we infer that the concave face of the LRR domains along with the N-terminal capping region participates in the interactions.

TLR2, TLR3, TLR4, CD14, caveolin 1, liposaccharide (LPS): CD14 and caveolin 1 are common TLR coreceptors. LPS is a ligand of TLR4. Decorin binds to TLR2 with a dissociation constant (Kd) of 59 ± 10 nM and to the TLR4-MD2 complex a Kd of 37 ± 5 nM [130]. Biglycan interacts with TLR4 and to a lesser extent with TLR2 [131,132]. Soluble biglycan is also a high-affinity ligand for CD14; the GAG chains are not required for binding to CD14 [133]. Lumican alone does not bind to TLR4, although lumican interacts with LPS [134]. Lumican also interacts with CD14 and LPS [135], and with CD14 and caveolin 1 [136]; CD14 binds LPS [137]. In the lumican-CD14 interaction, a critical role is played by Tyr20 of lumican [138]. The sequence of Y**F**KR**F**NA**L**QY in the LRR8 to LRR9 motif of lumican is a good candidate for Cav1 interactions [136]. Very recently, biglycan was identified as an endogenous TLR3 ligand [139]. The structure of the TLR4-MD-2/LPS complex indicates that LPS is bound to the hydrophobic pocket in MD-2 [140]. Sequence alignment indicates that lumican likely forms a hydrophobic concave face (Ala, Tyr, Trp, and Ile) in LRR1 − LRR3, although the tertiary structure is unknown still [9]. Taken together, we infer that LPS interacts with the concave face of lumican.

Cytosine – phosphate – guanine (CpG) dideoxynucleotide motif (CpG-DNA): Lumican competes with CD14 to bind CpG-DNA in vitro [136]. Biglycan binds CpG-DNA and suppresses TLR9 response [136]. TLR9 with 26 LRRs recognizes bacterial and viral DNA containing CpG-DNA [141]. The structure of the TLR9-CpG DNA complex reveals that CpG-DNA is recognized by both promoters, in particular by the N-terminal LRRNT–LRR10 fragment from one protomer and the C-terminal-terminal fragment (LRR20–LRR22) from the other [142,143]. Baumann et al., [144] suggested that CD14 binds to CpG-DNA directly, while Li et al., [145] disputed the claim that CD14 is involved in CpG DNA capture. We infer that CpG DNA may interact with the concave face of the LRR domain in biglycan.

Purinergic P2X4/P2X7 receptors: Biglycan simultaneously interacts with TLR2/4 and purinergic P2X4/P2X7 receptors, which activates the NLRP3 inflammasome [146]. The interaction of TLR2/4 with P2X7R/P2X4R occurs in the presence of biglycan. Taken together, we infer that the dimers of biglycan interact with TLR2/4 and P2X7R/P2X4R via the concave face and/or the ascending of biglycan.

Epidermal growth factor receptors (EGFR, ErBb2, and ErbB4): Epidermal growth factor receptor (EGFR) and insulin receptor (IR) families are both members of the receptor tyrosine kinase super family [147]. The EGFR ectodomain contains four domains - L1, CR1, L2 and CR2; the L1 and L2 domains are homologous. The L1 and L2 domains have five LRRs [148]. The EGFR family consists of EGFR (ErbB1/HER1), ErbB2 (HER2/EGFR2/Neu), ErbB3 (HER3), and ErbB4 (HER4). Decorin binds to EGFR, ErBb2, and ERbB4 [15,149-151]. Asporin interacts with ErBb2 and both form a complex [152]. Decorin binding was mapped to a narrow region of the EGFR within its ligand biding L2 domain [153]. The central part of LRR6 in decorin is required for interaction with the EGFR [153].

TGF-α: TGF-α belongs to the EGF family. Biglycan binds to TGF-α [154,155]. The structure of TGF-α consists of a third, N-terminal strand (residues 4–6) aligned with the large β-ribbon (residues 19–33) to form a three-stranded β-sheet and an ordered C terminus. The structure of the TGF-α − EGFR complex is available [156,157]; TGF-α molecule is clamped between the concave faces of the L1 and L2 LRR domains from the EGFR molecule. We infer that the binding site of TGF-α may be the concave face of the LRR domain in biglycan.

Insulin like growth factor (IGF) and insulin growth factor 1-receptor (IGF1R): The IGF-I system includes six binding proteins, three ligands (IGF-1, IGF-2, and insulin) and three major receptors of IGF1R, IR, and the IGF 2 receptor (IGF2R) [158]. The IR family that consists of IR, IGF1R and IR-related receptor forms two polypeptide chains, α and β. The ectodomains contain four domains of L1, CR1, L2 and CR, as seen in the EGFR family. The L1 and L2 regions of IGF1R have six and five LRRs, respectively [148]. Decorin binds IGF-1 [159]. Decorin also binds IGF-2 and insulin with high affinity, and, to a lesser extent, proinsulin and the insulin receptor A isoform (IR-A) [160]. Decorin [159-163], biglycan [164], and asporin [165] bind to IGF1R. PRELP directly binds to extracellular domains of IGF1R with low micromolar affinities [166]. Computational models of IGF1R and biglycan docking were proposed; none of the suggested complexes had the convex face of biglycan interacting with the receptor [164].

Low-affinity nerve growth factor receptor (p75NTR): p75NTR is a type I transmembrane protein and act as a tyrosine kinase co-receptor. PRELP directly binds to p75NTR with low micromolar affinities as well as IGF1R [166].

Ascending face

Fibronectin: Decorin interacts with the cell-binding domain of fibronectin [167] and also binds to the N-terminal fibronectin type III-repeat in collagen XIV [50]. Because heparin competed with decorin competitively, binding of decorin to fibronectin likely occurs at a heparin-binding region [168]. The sequence of NKISK in LRR3 (forming a part of ascending loop) of decorin is possibly involved in the interaction between the proteoglycan and fibronectin [169]. Fibromodulin also interacts with fibronectin [112]. In Silico analysis predicts that the fibromodulin-fibronectin interaction occurs on the entire concave face of fibromodulin [112].

Vesicular endothelial growth factor receptor 2 (VEGFR-2): Decorin binds VEGFR-2 [170,171]. Osteoglycin interacts with VEGFR2 [172,173], but not with VEGF-A. Decorin binds to the N terminus of VEGFR-2 in a region overlapping with its natural ligand VEGF-A [170]. The binding site of the decorin core protein includes 12 amino acid sequence LGTNPLKSSGIE in LRR5; most avid binding was represented by LGTNPLK at the proximal end [170]. The sequence constitutes an ascending loop in the LRR solenoid structure.

Complement factor (FH) and complement factor H-related protein-1 and -5 (FHR1 and FHR5): The complement system is a part of the innate immune system that enhances the ability of antibodies and phagocytic cells [174,175]. Human FH is composed of 20 complement control protein (CCP) domains. Fibromodulin [127], osteomodulin [128], chondroadherin [128] and PRELP [176] bind to FH. The Tyr-384/402 variant of FH binds fibromodulin better than the His-384 form [177]. The side chain of Tyr/His at position 384/402 is exposed to solvent [178]. Thus, we infer that π-π stacking interaction between neutral histidine in fibromodulin and aromatic amino acid Tyr-384 in FH occurs on the ascending loop face [102,179]. Fibromodulin, osteomodulin, and PRELP bind to complement factor H-related protein-1 and -5 (FHR1 and FHR5) [180]. FHR1 binds to these ECM components through its CCP domains 4-5, whereas FHR5 binds via its middle region, CCPs 3-7. Both FHRs competitively inhibit the binding of FH. Biglycan and decorin do not bind FH, FHR1, and FHR5 [180].

The N-terminal region

Decorin and biglycan have the extreme N-terminal region with GAG chains [7]. Fibromodulin and osteomodulin have N-terminal extensions with a variable number of O-sulfated tyrosine residues [30,31]. Strong ionic interactions are expected between GAGs and proteins. The main contribution to binding affinity comes from ionic interactions between the highly acidic sulphate groups and the basic side chains of arginine and lysine [181]. The interactions of GAGs with proteins also involve a variety of different types of interactions, including van der Waals (VDW) forces, hydrogen bonds, and hydrophobic interactions with the carbohydrate backbone [181].

The heparin-binding mycobacterial surface protein (HBHA): HBHA binds to decorin [182]. A truncated C-terminal HBHA fragment which contains Lys-Pro-Ala-rich repeats binds to decorin. This interaction likely occurs between the sulfated GAG extending from the decorin core protein and the Lys-Pro-Ala repeats at the C terminal side.

Integrins: Collagen fibrils can self-assemble [3,183]. The cell participates in organization of the fibrils through interactions involving integrins, fibronectin, thrombospondins, and tenascins [183]. Decorin directly interacts with α2β1 integrin [184,185], lumican with β1, β2, αM, αL, and α2β1 integrins [186-189], osteomodulin with αvβ3 integrin [190], and chondroadherin with α2β1 integrin [191,192]. The GAG moiety of decorin interacts with α2β, but not α1β1 integrin, at a site distinct from the collagen I-binding A-domain [184].

Tenascin X (TN-X): TN-X is an extracellular matrix protein whose absence results in an alteration of the mechanical properties of connective tissue [193]. TN-X consists of the N- to the C-terminal part by a Tenascin assembly domain (TAD), a series of 18.5 repeats of EGF-like motif, a high number of Fibronectin type III module, and a fibrinogen-like globular domain. The DS chains of decorin bind to the heparin-binding site included within the fibronectin-type III domains 10 and 11 of TN-X [194]. Interestingly, a binding site that interacted with the decorin core protein could be assigned to the N-terminal fibronectin type III repeat of collagen XIV [50]. In addition, an auxiliary binding site located C-terminal to this fibronectin type III repeat interacted with the GAG of decorin [50].

Low-density lipoprotein (LDL): LDL transports cholesterol and triglycerides from the liver to peripheral tissues. Decorin binds to LDL [195]. The GAG side chain of decorin is essential for LDL binding [196].

Decorin -binding proteins A and B (DbpA and DbpB): Two surface lipoproteins, DbpA and DbpB of the Lyme disease spirochete *Borrelia burgdorferi* bind decorin and GAGs [197-206]. DbpA and DbpB also bind biglycan only under flow condition [207]. GAGs are known to interact with Dbps through electrostatic interactions [206]. Lysine residues at the C-terminal sides of the Dbps are important in binding to decorin and GAGs [198-201,203,204]. Three lysine residues, Lys-82, Lys-163, and Lys-170 (referred to as the canonical binding GAG-residues) are critical for decorin binding [200,201]. In *B. garinii* SBK40 DbpA, Lys-80, Lys-161, and Lys-168 correspond to the canonical GAG-binding residues [206]. Multiple sequence alignment of the five homologs of Dbps shows that Lys-80 in DbpA and Lys-79 in DbpB are conserved, which indicates their importance of Dbp proteins [206]. Lys-78 and Lys-82 of DbpA, on the contrary, are part of the second potential binding site. The protein core of decorin may be required for detectable binding by DbpA [198,202]. However, there is yet no evidence of direct interactions between the decorin core protein and Dbps.

von Willebrand factor (vWF), matrilin-1, and chordin: vWF is a large protein with 2,813 amino acids and contains three types of VWF domains (vWFA 1-3, vWFC 1-3, and vWFD 1-4). Matrilin-1 contains two vWFA domains and one EGF-like domain. Chordin contains one vWFC domain. Decorin binds to vWF [208]. Decorin or biglycan interact with matrilin-1 [209]. Tsukushi binds to chordin [93]. Biglycan binds chordin and BMP-4 in Xenopus embryos [210]. The GAG side chains of decorin mediate the interaction with vWF [208]. The same binding mode may occur in biglycan. However, Tsukushi has no GAG chain. The structure of the complex of VWF A1 domain – the extracellular LRR domain of GP1bα reveals that the concave face is involved in the interactions [211, 212]. We infer that the vWF domain within chordin directly interacts with Tsukushi via its concave face.

p65NF-κB: Nuclear factor-kappa B (NF-κB) is an essential transcription factor in the control of expression of genes involved in cell growth, differentiation, inflammation, and neoplastic transformation. Biotin^{hbd} PRELP and p65NF-κB physically interact; the GAG-binding domain of PRELP acts as a cell type-specific NF-κB inhibitor that impairs osteoclastogenesis [213].

α–Dystroglycan: α-Dystroglycan is an extracellular peripheral membrane glycoprotein anchored to the cell membrane by binding to a transmembrane glycoprotein. *Torpedo* biglycan, in a fashion dependent on its CS side chains, binds to the protein core of the C-terminal third of α-dystroglycan [214].

Tumor necrosis factor-α (TNF-α): TNF-α is a cytokine that plays a central role in inflammation, immune system development, apoptosis, and lipid metabolism. TNF-α binds to both biglycan and decorin with Kds of 0.81 μM and 1.23 μM, respectively [215]. The binding occurs via both the core protein and the DS GAG chain.

C4b-binding protein (C4BP): C4BP is a complement, potent soluble inhibitor and contains many CCP domains [216]. Osteomodulin, chondroadherin, fibromodulin, and PRELP bind to C4BP [217]. The major interaction site on C4BP is localized to the central core, including CCP8. The binding of osteomodulin, fibromodulin, and PRELP to C4BP shows a concentration-dependent manner and ionic in nature, while the binding of C4BP to chondroadherin shows both ionic and hydrophobic character. PRELP and osteomodulin have overall basic and acidic properties, respectively, which are likely to contribute to their binding properties [217]. A cluster of tyrosine sulfate residues in the N terminus of fibromodulin contributes the anionic character of this SLRP, which may be important for the interactions [217]. Being basic, chondroadherin in contrast may use hydrophobic patches to bind C4BP as well as clusters of charged residues [217].

Heparin-binding proteins: The fibromodulin N-terminal domain binds motifs of basic clusters in heparin-binding proteins such as basic FGR-2, TSP-1, MMP13, the NC4 domain of collagen IX, interleukin-10, and PRELP [121]. Despite the differences in the tyrosine sulfate domain, binding to osteomodulin was the same as that to the fibromodulin tyrosine sulfate domain, with the interesting exception of MMP-13 [121]. The binding of the NC4 domain of collagen IX to fibromodulin and osteomodulin was also indicated by Kalchishkova et al. [218].

Thrombospondin-1 (TSP-1): TSP-1 contains heparin-binding domain, vWFc, laminin G-like, TSP type 1and 2, and the region of basic and acidic residues. Decorin interacts with TSP-1, which inhibits cell adhesion to TSP-1 [219,220]. The binding sites of decorin to TSP-1 are the GAG chains and the core protein [219,220]. Brain-specific angiogenesis inhibitors (BAIs) contain 4 to 5 TSP type-1 repeats (TSRs), while RTN4 (nogo)-receptors contain the LRR domain with nine LRRs. The structure of the BAI1 TSR3 domain in complex with RTN4 receptor revealed that a single TSR domain binds to the LRR domain of RTN4 receptor [221]. Thus, we infer that the LRR domain as well as the GAG chain participates in the binding to TSP-1.

CD44: The CD44 antigen is a cell-surface glycoprotein involved in cell–cell interactions, cell adhesion and migration. Biglycan interacts with CD44, which increases M1 autophagy [222]. Extracellular secreted asporin binds to CD44 to activate Rac1 [223,224]. The GAG chains of biglycan and lumican may interact with CD44, because CD44 interacts with the CS side chain of Serglycin [225].

Arginine clusters in PRELP and opticin

Perlecan: PRELP binds the basement membrane heparan sulfate proteoglycan perlecan and collagens [226]. PRELP contains Arg/Pro-rich amino acids at the extreme N-terminal side, as noted [30,31]. The N-terminal part of PRELP interacts with perlecan [226].

Heparin and heparan sulfate (HS): PRELP binds heparin and HS [227]. This interaction is mediated through the basic parts of highly sulfated sequences of heparin and heparan sulfate. Opticin binds to type XVIII collagen via its HS chains [228]. Opticin binds to heparin, HS, CS, and DS; the binding affinity is dependent on sulfation pattern and oligosaccharide chain [228]. We infer that the binding site of opticin is the arginine clusters of 153-RRTAYLYARFNRISRIR-159.

Platelet-derived growth factor (PDGF): Decorin binds PDGF [229,230]. Extractable pool decorin DS is able to bind most probably even in irreversible manner both growth factors (PDGF-BB and FGF-2) and fibronectin as judged from very low K_d values characterizing all interactions. In turn, biglycan DS displays particularly high affinity to FGF-2 [230].

The N-terminal capping region

Zn^{2+} and Ca^{2+}: Decorin is a Zn^{2+} metalloprotein [231]. The Zn^{2+}-binding sites are localized to the N-terminal domain of the core protein that contains 4 Cys residues. This likely results in a large conformational change of the N-terminal capping structure. The N-terminal polyaspartate domain of asporin binds calcium and regulates hydroxyapatite formation *in vitro* [66].

Fibrinogen: Fibrinogen is a glycoprotein complex that circulates in the blood of all vertebrates. Decorin binds with the globular D domain of fibrinogen in a Zn^{2+}-dependent interaction [232,233]. Taken together, the N-terminal capping region of decorin likely participates in the interaction with the fibrinogen D domain.

Myostatin: Myostatin is a member of the TGF-β protein family. Fibromodulin and decorin interact with myostatin [234-237]. Fibromodulin, fibronectin and laminin bind to myostatin in the presence of Zn^{2+} with $K_D = 10^{-10}$~10^{-8} mol/L [234]. Fibromodulin shows the highest affinity for myostatin among them. Myostatin binding to decorin requires Zn^{2+} binding to the N-terminal capping region of decorin [236,237].

α– and γ– sarcoglycan: The sarcoglycans are a family of transmembrane proteins (α, β, γ, δ or ε) involved in the protein complex responsible for connecting the muscle fiber cytoskeleton to the extracellular matrix. Biglycan binds to α– and γ–sarcoglycan but not β– or δ– sarcoglycan [238]. The binding sites on the polypeptide core of biglycan for α– and γ– sarcoglycan are distinct. α-Sarcoglycan binds to the N-terminal cysteine-rich domain of biglycan that forms a capping structure [238].

Lysyl oxidase (LOX): Lysyl oxidase (LOX) enzymes oxidize lysyl and hydroxylysyl residues from collagen and elastin chains [239]. Fibromodulin interacts with LOX and acts as a modulator of its activity fostering a site-specific cross-linking of collagen fibrils [74]. This interaction was mapped to the N-terminal 12 amino acids of fibromodulin with no apparent effect of tyrosine sulfation of fibromodulin [74].

The C-terminal region

CCN2/CTGF: CCN2 is a member of CCN protein family which is composed of four distinct domains connected in tandem, i.e., IGF-binding protein-like (IGFBP), von Willebrand type C, thrombospondin type 1 repeat (TSP-1), and C-terminal (CT) domains. Mouse Tsukushi binds to the CT and IGFBP domains of CCN2 [83]. Decorin interacts with CCN2 [236,240]. The interaction is in a saturable manner with a Kd of 4.4 nM and LRRs 10 – 12 are important for the interaction with CCN2 [240]. A peptide derived from the VS part of LRR12 (ie, Gln335-Lys359) inhibits CCN2 − decorin complex formation [240]. The part maps α-helix in the C-terminal capping structure. Thus, we suggest that the C-terminal capping structure participate in the interaction with CTGF.

Wnt-1-induced secreted protein 1 (WISP-1): WISP-1/CCN4 is a member of the CCN family of growth factors. Decorin and biglycan interact directly with WISP-1 [241].

Integrin α2β1: The binding site for integrin α2β1 maps to an α-helix in the C-terminal heparin binding region of chondroadherin (307–CQLRGLRRWLEAK–318) [192], which constitutes a part of the C-terminal capping structure. The core protein of lumican directly interacts with the I domain of α2 integrin subunit in the α2β1 integrin [189].

Heparan sulfate (HS): Chondroadherin contains the clusters of lysine or arginine at the very C-terminal side. It consists of 346-CKFPTKRSKKAGRH-359 [30,31]. The C-terminal part of chondroadherin binds to HS chains [242].

Transforming growth factor-β receptor 1 (ALK5): Lumican binds to ALK5 [243]. In silico analysis proposed that the interaction occurs between the C-terminal 50 amino acid region (L EKFDIKSFCKILGPLSYSK **I**KH**L**R**L**DGNR**I** SETSLPPDMYECLRV ANEVTLN) of lumican and the GS domain of ALK [243]; the lumican C-terminal region comprises a capping structure.

Apolipoprotein(a): Apolipoprotein(a) binds via its C-terminal domain to the protein core of decorin [244]. The binding of Lp(a) to decorin involves both electrostatic and hydrophobic interactions.

Core protein

Microfibril-associated glycoprotein-1 (MAGP-1) and fibrillin-1: MAGP-1 with 183 residues contains a disordered region in in the central, while fibrillin-1 with 2871 amino acids contains 48 EGF-like domains; these proteins are components of extracellular microfibrils. Decorin interacts with each protein individually and with both proteins together form a ternary complex [245]. The decorin core rather than its GAG side chain mediates the interaction. MAGP-1 interacts with biglycan but not decorin in the solution phase [246]. An EGF-like domain in fibrilin-1 might interact with the concave face of decorin.

Tropoelastin: Tropoelastin is the basic building block of elastin making up the majority of elastic fibers [247,248]. Tropoelastin is the soluble precursor of elastin with a molecular weight of about 60 kDa. Biglycan and decorin bind to tropoelastin [246]. The binding sites are contained in the protein cores of the proteoglycans rather than the GAG side chains [246]. Biglycan forms a ternary complex with tropoelastin and MAGP-1 [246]. Like hydroxyproline-rich collagen, elastin contains about one-third glycine and approximately one-ninth proline, and then is characterized by repetitive sequence. Thus, we think that elastin and tropoealstin partially adopt a collagen-like helix. Thus, tropoelastin adopting a collagen-like helix might interact through concave face of biglycan and decorin, as seen in the collagen interactions.

Filamin − A: Filamins are a family of actin-binding proteins composed of filamin A, B, and C [249]. The LRR region of decorin interacts with filamin-A (ABP-280) [250]. This interaction is dependent on the 288 carboxyl-terminal amino acids of filamin-A, which correspond to repeats 22–24 of its conserved β-sheet structure [250].

The CXC chemokine KC (CXCL1): CXCL1 that has chemotactic activity for neutrophils is a small peptide. CXCL1 forms homodimer [251,252]. The core proteins from lumican and keratocan directly interact with CXCL1 [253].

Smad2/3: Smad2/3 is a transcription factor. Asporin co-localizes and interacts with smad2/3 via the LRR domain [254]. Consequently, asporin facilitates its entry to nucleus, induces Epithelial-mesenchymal transition, and promotes cell invasion [254].

Tubulin: Tubulin consists of α- and β - subunits. α- and β - tubulins polymerize into microtubules, a major component of the eukaryotic cytoskeleton. Lumican interacts with tubulin [255,256]. The N-terminal part of lumican, and the fragments of spanning LRR1-LRP4, LRR5-LRR7 and LRP8-LRR10 are co-localized with microtubule [256]. Lumican core proteins interact with tubulins. Taken together, we infer that the binding sites might be the concave face of the LRR domain.

Resistin: Resistin is a cysteine-rich peptide hormone derived from adipose tissue [257]. Decorin lacking the glycation site binds to resistin [257]. This suggests that the decorin core protein interacts with resistin.

Covalent interaction

Aggrecan (Chondroitin sulfate proteoglycan 1): The aggrecan core protein is depicted with three disulphide bonded globular domains (G1-3), an interglobular domain (IGD), and attachment regions for keratan sulphate (KS) and chondroitin sulphate (CS1 and CS2). Aggrecan participates in covalent and nonreducible interactions with lumican in this high-molecular weight complex in the aging human sclera [258]. Theoretical model shows that lumican is covalently linked to the aggrecan through both disulfide bonding and the transglutaminase linkage of Gln-Lys (Q-K) [258].

Heat shock protein 47 (Hsp47): A collagen-specific molecular chaperon, Hsp47 of chicken directly interacts with decorin, lumican, and fibromodulin [259]. In the case of decorin and lumican, the interactions occur in intracellular locations, suggesting Hsp47 binds non-glycosylated SLRPs.

Unknown binding sites

SOX2 is a transcription factor that is essential for maintaining self-renewal or pluripotency of undifferentiated embryonic stem cells [260]. Tsukushi interacts with Sox2 and BMP-4 which controls stereocilia formation in the inner hair cells [92]. Delta protein from African clawed frog mediates segmentation of the paraxial mesoderm in Xenopus embryos [261]. It is 721 residues long and contains four EGF-like domains (UniProtKB: Q91902). Tsukushi interacts with Delta [83]. Fas ligand (FasL/CD95L) is a type-II transmembrane protein that belongs to the TNF family. Lumican has been suggested to bind FasL/CD95L [262]. Frizzled is a family of atypical G protein-coupled receptors that serve as receptors in the Wnt signaling pathway and other signaling pathways. Chick Tsukushi directly binds to the cysteine-rich domain of frizzled 4 with an affinity of 2.3×10^{-10} M and competing with Wnt2b [263]. Tsukushi also binds to frizzled 3 [264]. Wnt proteins are secreted glycoproteins that activate different intracellular signal transduction pathways. Podocan directly interacts with Wnt4 [265]. The receptor muscle-specific kinase (MUSK) is indispensable for nerve-muscle synapse formation and maintenance [266]. Biglycan directly binds the ectodomain of mouse MuSK [266]. Both the Ig and Frizzled (CRD/Fz) domains of MuSK are required for biglycan binding. 26S proteasome non-ATPase regulatory subunit 2 (PSMD2) is a component of the 26S proteasome, a multiprotein complex involved in the ATP-dependent degradation of ubiquitinated proteins [267]. Asporin strongly interacts with PSMD2 in gastric cancer (GC) cells [267]. Endostatin is a proteolytically released fragment of the C-terminal domain NC1 of collagen XVIII [263]. Endostatin binds biglycan and LDL [268]. Endostatin and biglycan interact with each other directly [268]. The crystal structure

of endostatin reveals a globular form [269]. The LRR domain of biglycan might interact with endostatin. p120 catenin regulates cell-cell adhesion with cadherins. Lumican interacts with nuclear p120 catenin [253,270]. Opticin binds retinal growth hormone in the embryonic vitreous [271]. Nyctalopin is located on the surface of photoreceptor-to-ON bipolar cell synapse in the retina [272]. Nyctalopin interacts directly with transient receptor potential cation channel subfamily member 1 (TRPM1) [273,274] and additionally with glutamate receptor mGluR6 [274]. Nyctalopin forms complexes with both TRPM1 and mGluR6 [274].

Discussion

The concave face, the ascending loop, the N- or C-terminal capping regions, the GAG chains, and/or sulfated tyrosine residues are involved in protein, protein interactions. Their combinations were shown or predicted. In contrast, the descending lateral face and the convex face were not observed in their interactions.

The structures of the EGF − EGFR complex (PDB:ID 3NJP and 1IVO) [275,276] are available. In addition, the structures of the IGF-1 − IGF1R and IGF-2 − IGF1R complexes (PDB:ID 5U8Q, 7S0Q, 6PYH, and 6VWI) have been determined [277-280]. To characterize the spatial arrangement of the two L-domains in EGFR and IGF-1R, Miyashita et al., [144] proposed two parameters of the distance between the two L domains (L) and the angle between the two axes showing the direction of the β-sheet stacking of the LRRs in the L domains (Ψ). The structural two parameters (L and Ψ) of their complexes in both the free state and the complexed state demonstrate that the EGF binding to EGFR and the IGF-1 or IGF-2 binding to IGF1R bring about large structural changes. Thus, we infer that similar structural changes occur in interactions between SLRPs (decorin, biglycan, asporin and PRELP) and EGFR or IGF1R.

The functions of SLRPs including decorin, biglycan and lumican are known to be altered in human diseases, such as cancers [16,281]. Lumican - derived peptides that interact MMP-14 inhibit melanoma cell growth and migration [236]. Decorin – derived peptide that interacts with CCN2 inhibits its biological activity [240]. Therefore, it would be significant to discuss the possibilities of blocking disease-related SLRP-ligand interactions as a targeted therapy. Drug delivery systems might be useful [282,283].

Conclusion

We undertook a comprehensive literature search of publications in order to make a list of ligands of all members of SLRPs. We discussed the interacting sites of SLRPs to the binding partners. The protein-ligand interactions occur on not only the concave face but also the ascending face and the N- or C- terminal capping regions. In addition, the extreme N- and/or C-terminal regions with the GAG chains or sulfated tyrosine residues participate in ligand-interaction.

Conflict of Interest

The authors of this manuscript declare that they have no conflicts of interest.

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Author Contributions

N.M did the design of research; H.M. and D.B. did structural analysis; N.M and R.H.K wrote the manuscript.

Competing Interests

The authors declare no competing interest.

Supplementary Materials

Table S1 shows the repeat number of LRRs of SLRPs and the helix parameters of the LRR solenoid structures.

Figure S1 shows the correlations of Δz and $2R\sin(\Delta\Phi/2)$ in the helix parameters of the LRR domains in SLRPs.

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