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Review

The role of small leucine-rich proteoglycans in osteoarthritis pathogenesis

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SUMMARY

Objective: To give an overview of the literature on the role of small leucine-rich proteoglycans (SLRPs) in osteoarthritis (OA) pathogenesis.
Method: A literature search was performed and reviewed using the narrative approach.
Results: (1) OA is an organ disease with many tissue types and specific roles for each in the pathogenic process. (2) Key biological functions of SLRPs include interacting with collagens to modulate fibril formation, and binding various cell surface receptors and growth factors to influence cellular functions; (3) Accumulating evidence has demonstrated the involvement of SLRPs in OA pathogenesis, most of which came from SLRP-deficient mice models; (4) Possible mechanisms for SLRPs being involved in OA pathogenic process include their roles in the extracellular collagen network, TGF-β signaling pathways, subchondral bone, muscle weakness, and the innate immune inflammation; (5) SLRP-deficient mice offer a potential to understand the molecular mechanisms of OA initiation and progression. (6) Targeting SLRPs may offer a new therapeutic modality for OA through controlling and modifying the TGF-β–ECM system. (7) Monitoring SLRP fragmentation may be a promising biomarker strategy to evaluate OA status.
Conclusions: Recent literature has shown that SLRPs may play an important role in OA pathogenesis. Possible mechanisms by which SLRPs are involved in this process have also been proposed. However, further investigations are needed in this field to better understand its mechanisms, develop treatments to slow down the degenerative process, and explore new approaches for effective and timely diagnosis of OA.

Introduction

Osteoarthritis (OA) is the most common joint disease in humans, affecting about 10% of the world population over 60 years of age[1]. It causes pain and disability, and is associated with substantial economic burden and serious socioeconomic consequences[2]. OA is a polygenic disease controlled by genetic and environmental factors, but its precise etiology is unclear. Although mainly characterized by the degradation of articular cartilage, it is best considered as a disease of the whole "joint organ"[3]. Evidence regarding functional aspects of the susceptible genes supports the view that all tissues within the joint may contribute to OA[4]. As for cartilage, injury, excessive wear and tear through overuse, as well as age, are strongly associated with the development of OA. It is also recognized that intra-articular derangement such as ligament transaction or meniscectomy is a risk factor for the onset and progression of OA. Moreover, OA is closely linked to the changes in the periarticular structures, such as skeletal muscle, tendon, and bone.

Epidemiological studies demonstrated that genetic factors are strong determinants of OA, and a few predisposing genes have been identified[5,6]. As a group of biologically active components of the extracellular matrix (ECM) of all tissues, small leucine-rich proteoglycans (SLRPs) have important effects on cell behavior, thus having implication in many biological functions[7]. Previous studies have revealed widespread involvement of SLRP genes in various pathogenic mechanisms causing skin fragility, osteoporosis, osteosarcoma, cardiovascular disease, and so on[8–10]. During the past one or two decades, evidence is surfacing for involvement of SLRPs in the pathogenesis of OA[8,11]. The following review will summarize the up-to-date knowledge about the role of SLRPs in OA pathogenesis, and propose several mechanisms as to how SLRPs can be involved in this process.

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Structure and classification of SLRPs

Proteoglycans (PGs) are widely distributed in all connective tissues and formed of glycosaminoglycans (GAGs) covalently attached to the core proteins. They have been classified into five families according to the structural properties of their core proteins[12]. One of such families is SLRPs, which were originally grouped on the basis of their relatively small protein core (36–42 kDa) in comparison with the larger aggregating PGs such as aggrecan and versican (more than 200 kDa), and on their unique structural organization composed of tandem leucine-rich repeats (LRRs)[7,12]. SLRPs can be generally described as two-part constructs. One part is N-terminal variable domain, and the other the conserved domain of LRRs [Fig. 1]. It was revealed that SLRPs are nonglobular, horseshoe-shaped, and solenoid-like molecules by molecular modeling and electron microscopy[13]. The horseshoe concave surface is formed by the LRR's β-sheets, whereas the LRR's α-helices and the SLRP's diverse carbohydrate moieties flank the convex surface[13]. Such structure is well suited for protein–protein interactions.

The rapidly growing SLRP family currently comprises 18 members, which are grouped into five distinct classes, including the traditionally defined classes I–III, and the non-canonical classes IV and V (Table I), based on such parameters as N-terminal Cys-rich clusters of the protein core and ear repeats, evolutionary conservation and homology at both the protein and genomic level, and chromosomal organization[14,15]. Regardless of the classification used, however, some SLRPs share common functionality[8]. Besides, diversity in composition enables SLRPs to facilitate protein–protein interactions with different cell and matrix components.

Key biological roles of SLRPs

When the first two SLRPs were cloned and sequenced about 25 years ago, they were only considered as one component of PGs[16]. Currently, it is well recognized that the SLRPs can be implicated in many biological functions, which have been extensively reviewed[14,17–19]. However, little is known about the involvement of SLRPs in OA pathogenesis.

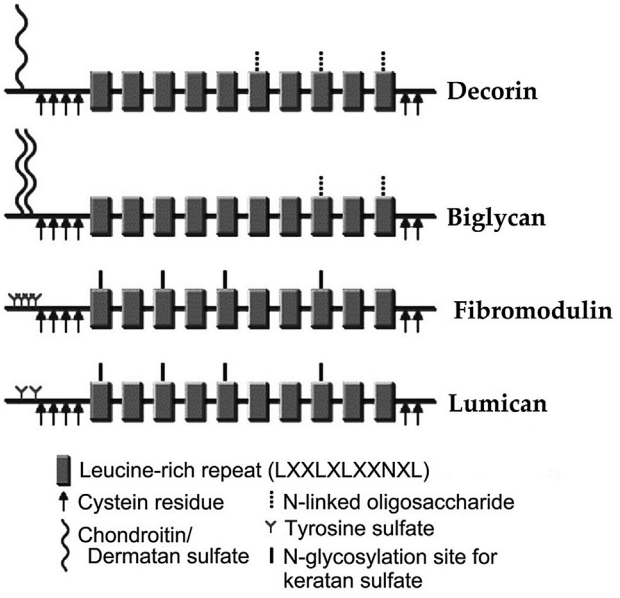

Fig. 1. Schematic presentation of the SLRP family members' molecular structure. The core protein of decorin, biglycan, Fmod or LUM is depicted with two disulphide bonded domains flanking ten LRR domains. In the case of decorin or biglycan, one or two CS/DS chains, respectively, reside in the amino terminal region. In the case of Fmod and LUM, one to four keratin sulphate chains (KS) may reside between the LRR domains (modified from Glycoword, www.gak.co.jp).

Table I
Classification, general structural characteristics, and distribution of SLRPs

SLRP (gene)	Protein core* (kDa)	GAG† (type)	Abundant in joint tissue
Class I			
Biglycan (BGN, PGS1)	38	CS/DS	Tendon, bone, cartilage, muscle
Decorin (DCN, PGS2)	36	CS/DS	Tendon, cartilage, muscle
Asporin (ASPN)	42		Periosteum
ECM2	77		
Uncharacterized new small leucine-rich proteoglycan on the human X chromosome (ECMX)	64		
Class II			
Fibromodulin (FMOD)	42	KS	Tendon, ligament, cartilage
Lumican (LUM)	38	KS	Cartilage, bone
PRELP	44	KS	Cartilage
Keratocan (KERA)	38	KS	Tendon, ligament, cartilage
Osteoadherin (OSAD)	42	KS	Bone
Class III			
Epiphycan (EPYC, PG-Lb, DSPG-3)	36	CS/DS	Cartilage, bone
Opticin (OPT)	35–45		Cartilage
Osteoglycin (OGN), mimecan (MIME), osteoinductive factor (OIF)	35	KS	
Class IV			
Chondroadherin (CHAD)	36	KS	Cartilage
Nyctalopin	50		
Tsukushi (TSK)	40		
Class V			
Podocan (PODN)	70		
Podocan like protein-1 (PODNL1)	57		

* The approximate molecular weight of protein core (kDa) without post-translational modifications.
† The type of GAG provided only by classical PGs (CS/DS: chondroitin sulfate/dermatan sulfate, KS: keratan sulfate).

The unique structure of SLRPs enables them to interact with a variety of other proteins[14]. Through interacting with collagens, they can modulate fibril formation[18] with convincing evidence from disorganized collagen fibrils in the SLRPs-deficient mice that consequently lose some connective tissue functions. Changes in the extracellular collagen network may cause the joint structures less suited to withstand physiologic mechanical loading, contributing to the development of OA. It is also speculated that different SLRPs may contain proteins for different stages of collagen fibrillogenesis[20,21]. Many SLRPs are therefore required for this process. In addition, regulation of collagen fibrillogenesis may not only be controlled by the expressions, but also by collagen-binding competition within the SLRPs. It is suggested that the SLRPs interact with collagen through specific binding sites[18]. Furthermore, various SLRPs may interact with collagen fibrils to form a "surface coat" as a steric barrier limiting the access of the collagenases to their cleavage site, and to regulate the physiology of collagenous matrices in a tissue-specific manner[22].

Another key role of SLRPs is that they are able to bind various cell surface receptors, growth factors, cytokines and other ECM components resulting in the ability to influence various cellular functions[14]. Through binding to extracellular components such as their ligands and receptors, SLRPs can directly regulate ligand-induced signaling pathways. Among them, the major targets of SLRPs are members of the transforming growth factor (TGF)-β superfamily pathways, including the bone morphogenetic protein (BMP) pathway[23,24]. Many recent studies have shown that SLRP members have the ability to regulate more than one signaling