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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.

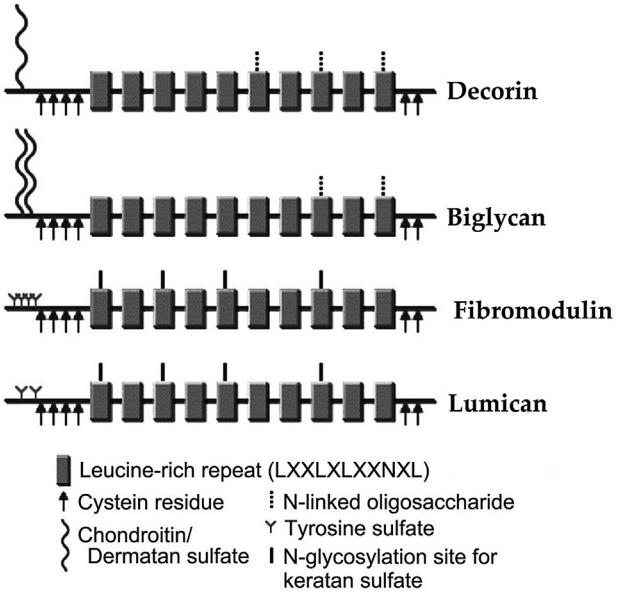

Fig. 1. Schematic presentation of the SLRP family members' molecular structure. The core protein of decorin, biglycan, Fmod or LUM is depicted with two disulphide bonded domains flanking ten LRR domains. In the case of decorin or biglycan, one or two CS/DS chains, respectively, reside in the amino terminal 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

pathway, thus directly and indirectly influencing cellular proliferation, migration, and phenotype[25,26]. It is also demonstrated that some SLRPs are essential in regulating cell biology, differentiation and migration behavior of mesenchymal stem cell-derived progenitor cells[27–29], which play important roles in OA pathogenesis[30,31]. What is more, SLRPs can be involved in activation of complement system[32] and Toll-like receptor (TLR) pathways[33], thereby having implications in chronic inflammatory processes and OA pathogenesis.

The involvement of SLRPs in OA pathogenesis

A large number of SLRPs are expressed in cartilage, including biglycan (BGN), chondroadherin (CHAD), decorin, epiphyean (EPN), fibromodulin (Fmod), keratocan, lumican (LUM), opticin (OPT), and proline/arginine-rich end leucine-rich repeat protein (PRELP)[34–36]. Additionally, the increased fragmentation of many SLRPs (BGN, decorin, Fmod, keratocan, and LUM) has been extensively reported in articular cartilage from age-matched OA joints compared with nonarthritic joints[37,38]. Many other studies demonstrated that chondrocytes increased the production of the SLRPs as an attempt to repair damaged ECM[37,39]. As such, it is suggested that the SLRP family members may be crucial to maintain normal chondrocyte activity and cartilage tissue integrity, and alterations in the distribution and production of SLRPs could lead to the development of OA[34,35].

Asporin (ASPN), a class I SLRP, was discovered in 2001 by Lorenzo *et al.*[34] and Henry *et al.*[40]. It was named based on the presence of a unique stretch of aspartate residues at its N terminus and the similarity with decorin[34]. However, unlike decorin and BGN, ASPN does not contain GAG chains. Its expression in cartilage of individuals with knee OA was greater than that of unaffected individuals[40]. Further *in vitro* evidence shows that ASPN acts as a negative regulator of chondrogenesis by inhibiting TGF-β function[41]. An association between the D-repeat polymorphism and Knee OA (KOA) susceptibility was ever demonstrated in the Han Chinese[42] and Japanese populations[41]. However, published results have been inconsistent. Positive association was not demonstrated in studies in Caucasians[43–45]. What is more, although strong association between D-repeat and knee OA in Asians was found in a meta-analysis[46], a subsequent study in Korean populations reported no difference in the frequency of the different ASPN alleles between the knee OA patients and the healthy controls[47]. It is due to the inclusion of this study that negative results were found in the two other recent meta-analyses[48,49]. More studies are required to draw the exact conclusion in Asian populations.

Previously, a lot of key information regarding the function and tissue expression pattern of SLRPs has been gathered from the available knockout (KO) mice, which can represent valuable *in vivo* models for various diseases[8]. Similarly, more and more investigations have used SLRP-deficient mice models and provided direct and valuable evidence for involvement of SLRPs in the pathogenesis of OA (Table II).

As shown in Table II, a large number of single and double SLRPs-deficient mice developed an OA-like change, including BGN-, Fmod-, and EPN-deficient, as well as BGN/Fmod, LUM/Fmod, and EPN/BGN double-deficient, suggesting that SLRPs may play an important role in maintaining joint integrity. The fact that many double SLRP-deficient mice display relatively severe phenotypes compared with their single SLRP-deficient counterparts[50–53] indicates that either these SLRPs have some overlapping functions within cartilage, or each SLRP has independent functions that, when deleted, exacerbate the progression of OA. Of note, although the single KO may have some features of the double KO, their mechanism of action could be different. For example, the absence of BGN may reduce induction of BMP-2 (to induce osteogenesis)[54], whereas, depletion of BGN and Fmod may increase BMP-2 causing osteogenesis in the tendon[50,55]. Interestingly, some SLRPs may compensate for the loss of others. For instance, the mRNA levels of three different SLRPs (ASPN, Fmod, and LUM) are increased in EPN/BGN double-deficient mice as compared with wild type mice[53]. A significant increase in LUM levels was found in cartilage, cruciate ligaments[52] and tendon[51] in Fmod-null mice. More BGN was also reported in decorin-deficient tendons[21], and more LUM in Fmod-deficient tendons[56].

Table II
OA-related phenotypes in KO mice

Ref	SLRP	Tissue(s) assessed	Phenotype
50	BGN Fmod BGN/Fmod	Knee tendon, cartilage	Collagen fibrils in tendons from mice deficient in BGN and/or Fmod are structurally and mechanically altered, resulting in unstable joints, tendon ossification and OA
51	LUM/Fmod	Knee tendon	The LUM/Fmod deficient mice displayed gait abnormality, joint laxity, and OA. Fmod acted as a key regulator and LUM as a modulator of tendon strength
52	Fmod	Knee cruciate ligaments	Cartilage degeneration in Fmod-deficient mice could be secondary to defects in the ligaments stabilizing the knee joint with no abnormalities in ECM of articular cartilage
53	EPN EPN/BGN	Knee cartilage	EPN plays an important role in maintaining joint integrity. The severity of OA phenotype in the EPN/BGN double-deficient mouse suggests a synergy between EPN and BGN
54	BGN Fmod BGN/Fmod	Knee ligament, tendon, menisci	At 3 months, all mutant mice displayed torn cruciate ligaments and EO in the targeted tissues. The phenotype was the least severe in the Fmod KO, intermediate in the BGN KO and the most severe in the DKO
55	BGN/Fmod	TMJ cartilage	Increased apoptosis of chondrocytes induced by the BGN and Fmod deficiency resulting in the early development of TMJ OA
56	BGN/Fmod	TMJ cartilage	Impairment in chondrocyte proliferation induced by the BGN and Fmod deficiency resulting in the early development of TMJ OA
57	BGN/Fmod	TMJ cartilage	The absence of BGN and Fmod disrupted the balance between ECM formation and degradation to the development of TMJ OA

DKO, double knockout.

Distinct *in vivo* function for each SLRP has been summarized in recent reviews[8,18], reflected by the distinct phenotypes developed by the different single deficient mice. Moreover, although various SLRPs are involved in OA development, their roles may be different from one another. Ezura *et al.*[20] showed mild and moderate alteration in collagen fibril structure of tendons in the LUM-null and Fmod-null mice, respectively. In another study[53], a progressive degeneration of articular cartilage was found in either EPN- or BGN-deficient mice model, but the onset of OA was observed at 9 and 6 months, respectively. Kilts *et al.*[55] also demonstrated that BGN deficiency resulted in a significantly more severe impairment of the soft tissues by 3 months of age in comparison with Fmod deficiency. Such differential impairment may arise from a functional difference between various SLRPs or due to a difference in SLRP composition between these tissues[51,55]. On the other hand, SLRPs deficiency appears to have joint type-dependent effect on the progression of OA. Mice deficient in BGN and Fmod developed OA in temporomandibular joint (TMJ) at 6 months, and by 18 months of age, there was almost complete destruction of the TMJ joint[57].

Comparably, in the knee joint of the same double-deficient mice, OA first appeared as early as 1–3 months, and by 6 months, there was almost complete destruction of the knee joint[50]. Such differences may be due to the differences in the anatomy and structure of the joints.

Possible mechanisms of SLRPs in OA pathogenesis

Although accumulating evidence demonstrates the involvement of SLRPs in OA pathogenesis, its precise mechanism is still unclear. The most striking pathologic change of OA is the progressive loss of articular cartilage. However, OA is not a disease of only articular cartilage, but involves all the tissues of the joint[3]. As SLRPs are present within the ECM of all connective tissues, and play important roles in the integrity of many musculoskeletal tissues, including bone, cartilage, ligament, tendon, *etc*, their involvement in the pathogenesis of OA may be through a single or combined ways depending on the type of SLRPs. The involvement of SLRPs in the development of OA may be associated with the following potential mechanisms [Fig. 2].

Changes in the extracellular collagen network

Depletion of SLRPs causes changes in the extracellular collagen network, making the joint structures less suited to withstand physiologic mechanical loading. Collagen loss was found at articular cartilage surface in both BGN-deficient and EPN/BGN double-deficient mice[53]. In addition, degenerative changes were detected in the cruciate ligaments of mice deficient in BGN[55], Fmod[52,55], and BGN/Fmod[55]. In parallel, an excessive number of very small collagen fibrils were observed in tendons of mice deficient in Fmod[51] and BGN/Fmod[50] compared with age-matched wild type mice. Importantly, these changes were present before OA started to develop, suggesting that such changes in collagen network in mutant animals may be responsible for increasing their susceptibility to develop knee OA.

Various SLRPs interact with collagen fibrils to form a "surface coat" to limit the access of the collagenases to their cleavage sites[22]. Since cleavage of the SLRPs may precede major destruction of the collagen, this would contribute to its interference with the network stability, preventing its repair and accelerating its degradation[58,59]. A number of matrix metalloproteases (MMPs) are able to cleave SLRPs[11]. As MMP-13 was demonstrated to play a major role in cartilage degradation, Monfort *et al.*[59] investigated its ability to cleave members of two classes of SLRPs: BGN and decorin, as well as Fmod and LUM, and found extensive cleavage on Fmod and BGN. This suggests that SLRP degradation induced by MMP-13 may represent an early critical event in the process of cartilage degradation, by exposing the collagen fibrils to proteolytic attack and permitting subsequent cartilage degeneration.

TGF-β signaling pathways

SLRPs may bind with and modulate members of TGF-β superfamily, which are necessary for integrity of cartilage, tendon and ligament. TGF-β, a key regulator of chondrocyte differentiation and proliferation, has an important role in the pathogenesis of OA[60]. The binding of SLRPs to members of the TGF-β family may regulate their activity by sequestering them into the ECM, thereby preventing their binding with the cellular receptors. Nevertheless, SLRP/growth factor interactions are quite complex, whether SLRP help or hinder growth factors depends on the tissue context[17]. In this context, whether TGF-β "bad" or "good" for joint health may relate to the use of the SLRP models.

Prior to the onset of OA, decrease in chondrocyte number was commonly observed in knee articular cartilage in BGN-deficient and EPN/BGN double-deficient mice[53], as well as in both knee articular cartilage and TMJ fibrocartilage in fibromodulin/BGN double-deficient mice[57,61]. ASPN was also found to work as a negative regulator in chondrocyte differentiation and cartilage ECM formation through suppressing TGF-β–mediated expression of the genes aggrecan and type II collagen to reduce proteoglycan (PG)

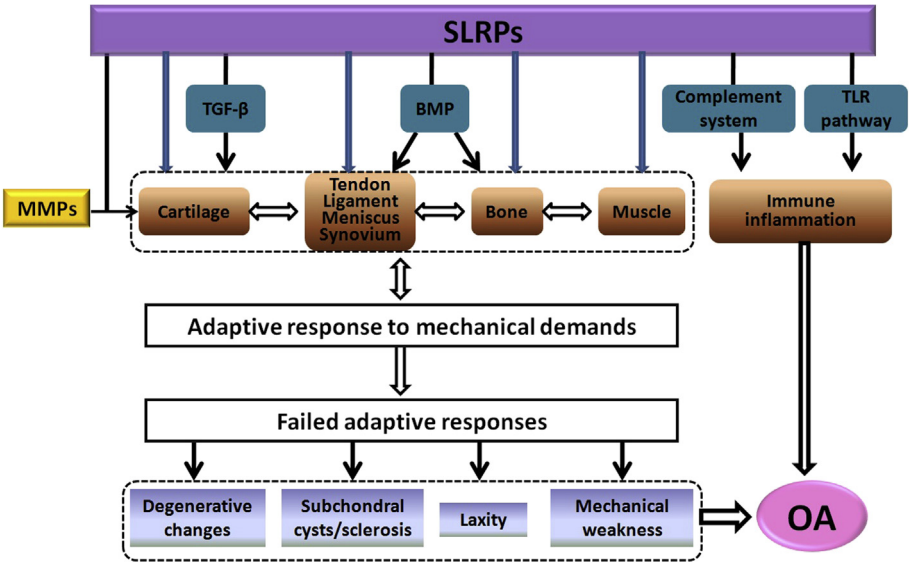

Fig. 2. A mechanistic model depicting how absence of SLRPs leads to OA. Firstly, depletion of SLRPs may cause cartilage destruction in many ways, such as changes in the extracellular collagen network, and impairment in chondrocyte proliferation through modulating TGF-β activity. Additionally, various SLRPs interact with collagen fibrils to form a "surface coat" to limit the access of the collagenases to their cleavage sites. SLRP degradation induced by MMP may affect the collagen network by exposing the MMP cleavage site in this macromolecule. Secondly, depletion of SLRPs may cause an excessive number of very small collagen fibrils and degenerative changes in tendon and ligament, leading to joint instability. In addition, EO is extensively detected in soft tissues, including meniscus, ligament and tendon, through regulating BMPs, which is correlated to the development of OA. Other possible mechanisms include altered subchondral bone structure and muscle dystrophy secondary to the depletion of SRLPs. Finally, SLRPs can be involved in activation of complement system and TLR pathways, thereby having implications in OA pathogenesis.

accumulation[41]. As such, the impairment in chondrocyte proliferation induced by SRLPs deficiency could be a key event in the early development of OA. In the bone marrow stromal cells from BGN/decorin double-deficient mice, an increase in TGF-β activity was reported by Bi *et al.*[62]. Embree and colleagues[63] further demonstrated that the sequestration of TGF-β1 was decreased within the ECM of BGN/fibromodulin deficient mandibular condylar chondrocytes (MCCs), leading to overactive TGF-β1 signal transduction, chondrogenesis and ECM turnover.

On the other hand, ectopic ossification (EO) was extensively detected in soft tissues, including meniscus, ligament and tendon, in mice deficient in BGN[53,55], fibromodulin[55], BGN and fibromodulin[50,55], as well as EPN and BGN[53]. The formation of EO can be seen as a localized attempt to compensate for the original decreased stiffness of tissues. Due to ECM "microdamage", the SLRP-deficient tissues may respond to external forces by changing their compositions. The fact that additionally forced use of the joint increases EO and OA in the BGN/fibromodulin double mutants supports this mechanistic model[50,55]. It is proposed that BMPs are involved in the formation of EO[55,62]. tendon stem/progenitor cells (TSPCs) were found to reside within a unique niche predominantly comprised of the ECM[62]. The normal ECM-rich niche controls the BMP activity so that TSPC can differentiate into tenocytes that form tendon. However, depletion of BGN and fibromodulin can affect the differentiation fate of TSPC by stimulating the BMP signaling pathway[62]. Recently, Kilts *et al.*[55] also proposed that tendons depleted of BGN or fibromodulin may fail to bind and regulate BMPs, and this unregulated BMPs activity would lead to more stimulation of TSPCs by BMPs causing them to form ectopic bone instead of normal tendon.

Roles in subchondral bone

OA arises indirectly from the altered subchondral bone structure. The role of subchondral bone is currently believed to be of particular importance in the pathogenesis of OA[64]. Although convincing evidence is lacking to support this notion, there are substantial data to show the important role of some SLRPs in bone formation. For example, compared with wild-type mice, BGN-deficient mice displayed slow bone growth and reduced bone mass due to a significant decline in osteoblast number and progressive depletion of the bone marrow stromal cells[54]. Chen *et al.*[29] further suggested that the development of age-related osteopenia in BGN-deficient mice may be attributed to a defect in the quantity and quality of osteoblastic progenitors resulting from the altered expression of sets of genes associated with cell cycle, cell growth, and differentiation. It was also reported that male EPN-deficient mice had significantly shorter femurs than wild type mice at 9 months[53]. In addition, the class II SLRP, PRELP, may impair osteoclastogenesis to prevent osteopenia[65].

Muscle weakness

Muscles and joints are functionally interdependent, as muscles stabilize joints and contribute significantly to their loading. Muscle weakness is an acknowledged associate of joint degeneration and OA[66]. In a rabbit model[67], botulinum toxin type-A induced quadriceps weakness was found to cause increased degeneration in the retro-patellar cartilage, providing evidence that muscle weakness might be a risk factor for the onset and progression of OA. Tonge *et al.* further reported that disease initiation in the ageing guinea pig model of OA is coincident with altered expression of mRNAs associated with quadriceps skeletal muscle contractile properties[68]. Therefore, another possible explanation is that OA arises indirectly from the induced muscle dystrophy. A number of studies have shown that BGN binds and regulates some components of DAPC (dystrophin-associated protein complex) and may play a role in muscular dystrophies[69]. A mild muscular dystrophic phenotype was displayed in mice deficient in BGN characterized by membrane disruption and cell death of a subpopulation of myofibers[70]. As for decorin, different roles were reported during skeletal muscle formation and repair. This protein inhibits the expression of myogenin, a muscle-specific transcription factor, which promotes myoblasts differentiatio[71]. It was also reported to modulate myoblasts proliferation *in vitro* through binding myostatin[72], a member of the TGF-β family of growth factors. Decorin sequesters myostatin in the ECM, thus favoring myogenic cell proliferation and differentiation.

The innate immune inflammation

As a whole joint disorder, OA affects all joint tissues that communicate at the cellular level by releasing and responding to inflammatory mediators. Synovial inflammation is increasingly recognized as an important pathophysiologic process in OA. The complement system, a crucial part of the innate immune defense, is found to be associated with the chronic inflammation in OA[73]. Recently, a role of SLRPs has been proposed in the regulation of complement activation in diseases involving the ECM, particularly those characterized by chronic inflammation, like OA[32]. Fibromodulin or LUM can directly bind to C1q and activate the classical pathway of complement[32,74]. However, BGN, along with decorin, can function as an anti-inflammatory protein by binding to and blocking the complement protein C1q, thereby inhibiting activation of the complement cascade and proinflammatory cytokine production at the tissue level[75].

Activation of TLR pathways may also play a central role in the development and progression of OA[76]. A role has been suggested of signaling molecules and crucial proinflammatory factors in some SLRPs. For example, BGN acts in macrophages as an endogenous ligand of TLR4 and TLR2, and stimulates the expression of tumor necrosis factor alpha (TNF-a) and macrophage inflammatory protein-2 (MIP-2) via activation of p38, ERK, and NF-kappaB[33]. LUM is also involved in innate immune response by affecting TLR4 signaling pathway. LUM-deficient macrophages show impaired response to lipopolysaccharides resulting in lower induction of TNF-a and interleukin-6[77]. Although SLRPs have potentials as key modulators of the OA microenvironment, additional studies need to be performed to understand the relationships of the SLRPs with complement system and TLRs, as well as their roles in the development and progression of OA.

Conclusions and future directions

In this review, up-to-date information has been gathered to analyze the involvement of many SLRPs in the development of OA. It is well known that a large number of single or double SLRPs-deficient mice can develop an OA-like disease. Although OA is a major cause of disability in the ageing population with an increasing prevalence and influential social consequences[1], fundamental treatment for OA is lacking. Current therapy for OA is largely palliative, mainly focusing on alleviation of symptoms. Therefore, numerous OA animal models have been developed aiming at better understanding the mechanisms, developing new strategies to slow down the degenerative process, and exploring effective and timely diagnosis of the disease.

OA models have been induced by many methods in a variety of animal species[78]. Among them, genetically-modified mice offer a potential to understand the molecular mechanisms of OA initiation and progression. Since OA is thought to be a multifactorial

disease, it is necessary to use multiple murine models, including SLRP-deficient mice, to best understand OA disease progression. As various SLRPs single- and double-deficient mice develop OA, such mutant mice provide important new tools to investigate the molecular mechanisms underlying this disease. Importantly, the SLRP-deficient mice model with a wide variety in progression rate of OA is currently advantageous over any other animal model. For instance, the BGN/fibromodulin double-deficient mouse presents an earlier and faster progression of OA, making it a model of choice for rapid advances in OA research. On the contrary, a more slowly evolving OA with comparable etiology can be investigated in the BGN or fibromodulin single-deficient mouse. Indeed, many findings from these SLRP-depleted mouse models have shed light on how SLRPs influence the molecular events that lead to OA[53]. TGF-β interacts with a number of cartilage ECM proteins. The functional link between ECM proteins, TGF-β activity and OA has been indicated by a number of studies on SLRPs[34,63]. This suggests that agents controlling and modifying the TGF-β–ECM system are promising targets for treatment, thus offering a new therapeutic strategy for OA. The dichotomy of TGF-β effects is noteworthy in different joint tissues. While its induction of a chondrogenic response can be viewed as cartilage reparative, TGF-β can also trigger problems in other tissues of the joint and results in fibrosis and osteophyte formation[60]. SLRPs may function to regulate the beneficial vs harmful effects of TGF-β signals[63]. It is therefore of great interest to understand how SLRPs might modulate these aspects of TGF-β induction, and which SLRPs might be most important in repair of chondroid or fibrogenic tissues, before an SLRP-targeted therapeutic modality can be anticipated.

As aforementioned, the majority of current findings came from SLRP-deficient mice models regarding the involvement of SLRPs in the pathogenesis of OA. However, little is known about the possible role of SLRPs in validated murine OA-like models. It should be noted that the molecular mechanisms of both joint structural damage and pain may be distinct in animal models of OA induced or initiated by different means[78]. Obviously, an important distinction exists between murine SLRPs deficiencies and murine OA-like models (with a single precipitating event such as joint injury) since the SLRP deficiencies described are conventional KOs and therefore the pathology is bound to be influenced by developmental and growth abnormalities. Humans with such abnormalities represent a very minor group of the OA population. As such, more investigations using multiple OA animal models are necessary to enrich our understandings in this aspect. However, subsequent interpretation of the data and its extrapolation to the human condition must be more precise[78].

At present, diagnosis of OA can be made by imaging techniques only after irreversible damage to the joint occurs. As cartilage has a limited capacity to regenerate, it should be beneficial to detect and treat OA at an earlier stage. A variety of OA-associated protein fragments have been reported as possible biomarkers to evaluate cartilage metabolism or OA progression, including some SLRPs fragments[35–37,79,80]. Monfort *et al.*[59] demonstrated the ability of human recombinant MMP-13 to cleave BGN and fibromodulin extensively, and characterized a novel major cleavage site for BGN. The susceptibility of cartilage SLRPs catabolites during cartilage destruction was further highlighted by Young and colleagues[81], who advocated a strategy of monitoring SLRP fragmentation as a promising biomarker strategy to evaluate OA status. It will be of substantial interest to ascertain whether OA-associated alterations in usurped SLRP fragments correlate with disease severity, and to ultimately detect some SLRP core protein fragments as valuable biomarkers for joint disease initiation and development.

Author contributions

All authors discuss the concept of the manuscript. GXN wrote the manuscript. ZL and YZZ prepared some materials. All authors edited and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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