Osteoarthritis and Cartilage xxx (2015) 1–7

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

Asporin and osteoarthritis

L. Xu, Z. Li, S.-Y. Liu, S.-Y. Xu, G.-X. Ni*

Department of Orthopeadics and Traumatology, Nanfang Hospital, Southern Medical University, China

ARTICLE INFO

Article history:
Received 20 November 2014
Accepted 8 February 2015

Keywords:
Asporin
Small leucine-rich repeat proteoglycans
Osteoarthritis

SUMMARY

Objective: To provide an overview of the literature describing the role of asporin, a small leucine-rich proteoglycan (SLRP), in osteoarthritis (OA).
Method: A literature search was performed and reviewed using the narrative approach.
Results: As a class I SLRP member, asporin, is distinct from other SLRPs. Accumulating evidence demonstrates the involvement of asporin in OA pathogenesis. Many human studies have been conducted to explore the association between the D-repeat polymorphisms and OA susceptibility, but these yield inconsistent results. Possible mechanisms for the involvement of asporin in OA pathology include its influence on TGF-β (transforming growth factor-β) signaling pathways and collagen mineralization. To date, no studies were found to use an asporin-deficient animal model that would help to understand disease mechanisms. Many issues must be addressed to clarify the link between asporin and OA to provide a novel therapeutic strategy for OA, perhaps through controlling and modifying the TGF-β-ECM system.
Conclusions: Studies examined demonstrate the involvement of asporin in OA pathogenesis, and possible mechanisms by which asporin may be involved in this process have been proposed. However, large-scale interracial studies should be conducted to investigate the association between asporin and OA, and further investigations are needed to obtain a better understanding of the disease mechanism, develop novel therapeutic strategies, and explore new approaches for diagnosis of OA.

Introduction

As the most prevalent form of arthritis in humans, osteoarthritis (OA) is the leading skeletal disease that causes disability after middle age. In the United States, over 25 million people suffered from clinical OA in 2005[1]. It is estimated that 15.4% and 42.8% of Chinese females aged 60 years or older could be diagnosed as symptomatic and radiographic knee OA, respectively[2]. Unfortunately, however, current therapeutic approaches only slow progression of OA rather than prevent it. Although its etiology remains unknown, it is believed that OA is a polygenic disease controlled by genetic and environmental factors[1,3]. Some genetic linkage and candidate genes have been reported to be associated with susceptibility to OA, suggesting that genetic factors play an important role in its development[4]. The roles of small leucine-rich proteoglycans (SLRPs), a group of biologically active components of the extracellular matrix (ECM) of many tissues, in OA pathogenesis have recently been reviewed by our group[5].

Like many other SLRPs, asporin, a class I SLRP, exerts an important influence on cell metabolism, including cell differentiation, proliferation, migration, and apoptosis[6,7]. Previous studies revealed the involvement of asporin in the pathogenic mechanisms of disc degenerative disease[8] and periodontal disease[9,10]. The following review will summarize the recent literature concerning the role of asporin in OA pathogenesis, and the potential mechanism by which it might be involved in this process.

Structure and tissue distribution of asporin

The growing SLRP family comprises 18 members, which are grouped into five distinct classes, based on the structural properties of their core proteins[5]. Asporin was first discovered and named in 2001 by Lorenzo *et al.*[11] and Henry *et al.*[12]. It was simultaneously and independently discovered by Yamada *et al.*[10], and identified as “periodontal ligament-associated protein 1(PLAP-1)” because it was specifically expressed in the periodontal ligament (PDL).

* Address correspondence and reprint requests to: G.-X. Ni, Department of Orthopeadics and Traumatology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. Tel: 86-20-61641744; Fax: 86-20-62787924.
E-mail address: fgxni@graduate.hku.hk (G.-X. Ni).

http://dx.doi.org/10.1016/j.joca.2015.02.011
1063-4584/

The gene that encodes asporin protein lies within a gene cluster on human chromosome 9q22-9q21.3, which contains the ECM protein 2 gene, osteoadherin (class II SLRP) and osteoglycin/mimecan (class III SLRP) genes[12,13]. Similar to two other class I SLRP members (decorin and biglycan), asporin contains an internal stretch of 10 tandem leucine-rich repeats (LRR) (Fig. 1), each of which contains 20–30 amino acids and is inserted by leucine residues in fixed conserved regions. Asporin consists of 380 amino acids, and it contains a putative propeptide, four cysteines on the N-terminus and two cysteines on the C-terminus[11]. Notably, the N-terminal regions of decorin and biglycan are substituted with one and two chondroitin/dermatan sulfate chains[14,15], respectively.

Although its amino-acid sequence is 50%/70% identical to that of decorin/biglycan[12,14], asporin differs from these two class I SLRPs (Table I). Asporin has distinguishing characteristics: (1) it possesses a unique stretch of aspartic acid residues (D-repeat) in its N-terminal region. The number of D-repeats varies from 9 (D9) to 20 (D20), and each variant with a different number of D-repeats may play a different role in OA pathogenesis (discussed below)[9,11,14]. (2) It does not fit the strict definition of a proteoglycan because there is no consensus sequence for glycosaminoglycan attachment between the propeptide and the amino-terminal cysteine motif[11,12,16] (Fig. 1 and Table I).

Asporin protein has been found to be expressed in many tissues. In mouse embryos, it is expressed in perichondrium or periosteum of maxilla, vertebrae, mandible, and long bones, but not in epiphyseal cartilage[12,14]. In humans, it is expressed in aorta, uterus, heart, liver, and abundantly in articular cartilage[9,11,12,17], PDL, and dental follicle[18,19]. A recent proteomic study reported that asporin content in meniscus is much higher than in the medial tibial condyle and the femoral head cartilage[20]. Like decorin and fibromodulin[21], asporin directly binds TGF-β, and, subsequently, binds to collagen by way of its LRR domain. Its N-terminal extension remains available to interact with other matrix constituents, including fibers of collagen, thus playing a role in collagen fibrillogenesis and metabolism[11,17].

Table I
Characteristics of asporin, decroin and biglycan

	Asporin	Decorin	Biglycan
Gene location	9q22-9q21.3	12p[76]	Xq28-ter[76]
Proteoglycan?	No[12]	Yes[64]	Yes[77]
Abundant in joint tissue	Periosteum, PDL, liver, heart, aorta, uterus, predentin	Tendon, cartilage, muscle, skin, kidney, muscle, predentin	Skin, tendon, bone, cartilage, PDL, kidney, muscle, predentin
Protein core	42	36	38
Upregulated in diseases	OA, Scleroderma, DDD	Osteogenesis imperfecta, Ehlers-Danlos syndrome, OA[8,11]	Fibrosis and atherosclerosis
TGF-β Binding sites	P33-373(mainly),33-167, P48-167,P279-373[53]	P155-260(mainly), P45-359, P63-190[78]	P208-216[79]
Collagen binding sites	The 10–12th LLR[63]	The 4–5th[80], 6th LLR[81],	
Factors related to expression	TGF-β,BMP	TGF-β,EGFR,RTK, MET,IGF-IR[21]	TGF-α/TGF-β, IL, TNF-α,BMP[79]

Involvement of asporin in OA pathogenesis

Evidence suggests the involvement of asporin in OA pathogenesis. Asporin expression is increased in OA cartilage as compared with normal cartilage[16]. Further, *in vitro* evidence shows that asporin acts as a negative regulator of chondrogenesis by inhibiting TGF-β function[20]. More direct evidence comes from human studies, which investigated the association between D-repeat polymorphisms and OA susceptibility (Table II). However, the findings reported were contradictory. In Japanese and Chinese Han populations, D14 was found to be a risk factor in development of knee OA while, D13 was found to be a protective factor against OA in some Japanese[22,23]. However, similar associations with knee/hip OA were not demonstrated among Caucasians in the United States[24] and Spain[25], and a weak association was detected in Caucasian men who had undergone knee replacement surgery in the United Kingdom[26]. Moreover, asporin was found to be associated with hand OA in the Netherlands[27]. An association with D-repeat polymorphisms was also confirmed for knee OA in a Greek population[28,29]. Further, other alleles (D12, D15, or D16) were associated with OA either as a risk factor or a protective factor in Mexican[30] and Iranian[31] study populations. Despite positive associations found in some study populations, when data are stratified by ethnicity, the results of

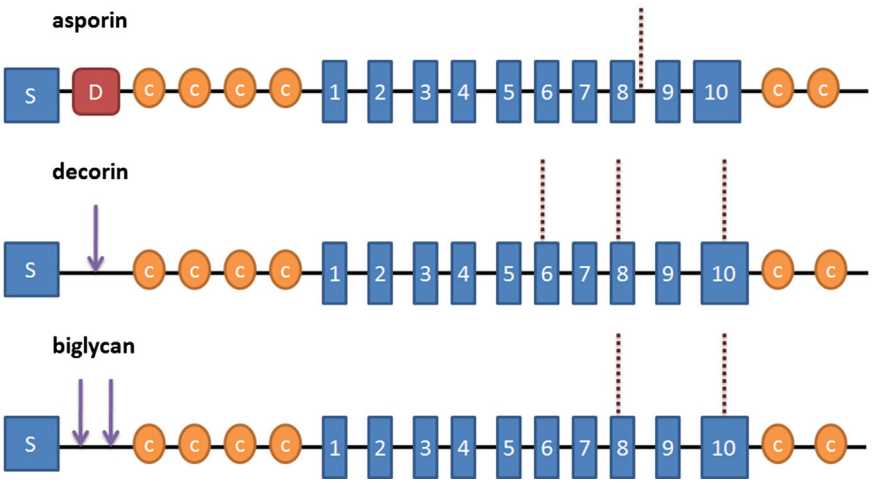

Fig. 1. Schematic diagram of class I SLRP molecular structure. The structure of asporin is similar to that of decorin and biglycan in that they all have LRR, cysteine regions on both N- and C-termini, and signal peptides in the N-terminus. However, asporin is not a proteoglycan because of the absence of a glycosaminoglycan attachment site. Moreover, asporin may present different characteristics that depend upon the number of aspartatic acid residues. S: signal peptide; D: aspartic acid (D)-repeats; C: cysteine region; Blue box: LRR; dashed line: N-linked glycosylation site; arrow: O-linked glycosylation site.

Please cite this article in press as: Xu L, et al., Asporin and osteoarthritis, Osteoarthritis and Cartilage (2015), http://dx.doi.org/10.1016/j.joca.2015.02.011