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Review

Galectin-3: A key player in arthritis

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ABSTRACT

Arthritis is more and more considered as the leading reason for the disability in the world, particularly regarding its main entities, rheumatoid arthritis and osteoarthritis. The common feature of arthritis is inflammation, which is mainly supported by synovitis (synovial inflammation), although the immune system plays a primary role in rheumatoid arthritis and a secondary one in osteoarthritis. During the inflammatory phase of arthritis, many pro-inflammatory cytokines and mediators are secreted by infiltrating immune and resident joint cells, which are responsible for cartilage degradation and excessive bone remodeling. Amongst them, a β-galactoside-binding lectin, galectin-3, has been reported to be highly expressed and secreted by inflamed synovium of rheumatoid arthritis and osteoarthritis patients. Furthermore, galectin-3 has been demonstrated to induce joint swelling and osteoarthritis-like lesions after intra-articular injection in laboratory animals. However, the mechanisms underlying its pathophysiological role in arthritis have not been fully elucidated. This review deals with the characterization of arthritis features and galectin-3 and summarizes our current knowledge of the contribution of galectin-3 to joint tissue lesions in arthritis.

1. Introduction

Arthritis is mainly composed of rheumatoid arthritis (RA) and osteoarthritis (OA). Pain, inflammation and stiffness of the joints are the main common symptoms leading to disability, whereas bone changes vary from subchondral sclerosis and osteophytosis in OA to erosions and osteoporosis in RA. In France the prevalence of radiographic OA was estimated of about 17% and a recent study indicates that the prevalence of symptomatic knee OA is around 2% for both males and females of 40 to 49 years-old, while increasing to 10 to 15% for people between the age of 70 to 75 years [1]. In contrast, the RA prevalence is 0.3% in France [2].

The aetiology of each disease is different, as RA is an autoimmune inflammatory disease while OA is generally considered as a degenerative/mechanical one. In addition, genetic and environmental influences do not overlap between diseases, while autoantibody production is restricted to RA. However, inflammation of the synovial membrane is a prominent feature of OA pathogenesis that results in synovitis, which is thought to reflect structural progression of OA [3]. Synovial inflammation is a primary event in RA whereas it can be an early, as illustrated by tissue thickening detected by MRI [4] or a late event, secondary to cartilage breakdown, in OA. Although synovitis is frequent in OA, the level of inflammation remains lower than in RA and pannus formation occurs scarcely, whereas it is a major characteristic of RA [5]. Such grading of inflammation comes from the much lower contribution of cells of the innate (mainly phagocytes) and adaptative (B and T lymphocytes) immune responses in OA than in RA. Synovitis induces cartilage destruction and accounts for bone erosion in RA while promoting subchondral bone (SCB) remodeling in OA. Within the pannus, where leukocyte infiltration occurs beside proliferation of the synovial lining, pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) are secreted into the joint. Another soluble factor, galectin-3 (gal-3), is markedly present in synovial tissue during the inflammatory flares. Of note, gal-3 is found in much higher concentrations in RA than in OA synovial tissue [6]. In addition, genetic polymorphisms of galectin-3 may influence the susceptibility to RA, as the galectin-3

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gene allele (LGALS3 +292C) is more prevalent in RA patients than in healthy controls [7].

In this mini-review, we will summarize some properties of gal-3 and present available data supporting its pathophysiological role in the different joint tissues, namely synovium, cartilage and subchondral bone during arthritis.

2. Galectin-3: a peculiar member of the galectin family

Galectins are a family of evolutionary conserved animal lectins, which share a high degree of homology in the amino acid sequence of their carbohydrate-recognition domain (CRD). Another common characteristic of these lectins is their affinity for β-galactosides. To date, 15 galectins have been discovered and classified into three distinct subgroups based on the number and organization of their CRDs (Fig. 1).

Prototypic galectins (galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15) contain one CRD and are able to homodimerize. The prototypic galectin-1 is one of the most extensively pro-tumorigenic galectin studied. Its concentration in blood has been demonstrated to correlate with cancer progression in a number of studies. More interestingly, this correlation can be disrupted, for therapeutic purpose, by injection of molecules able to block the CRD activity [8].

Tandem repeat type galectins (galectin-4, -6, -8, -9 and -12) consist of a single polypeptide chain that forms two distinct but homologous CRDs, separated by a linker composed up to 70 amino acids.

Gal-3, which has been called Mac-2 when first discovered in macrophages, is the unique chimera type in the family of galectins. It was found to be widely distributed in tissues, including gut, brain, kidneys and skeleton [9]. Probably as the best studied member of the galectin family, gal-3 has been shown to amplify inflammatory responses [10] and to play key pathophysiological roles in several biological processes including angiogenesis [11] and development or progression of tumors [12].

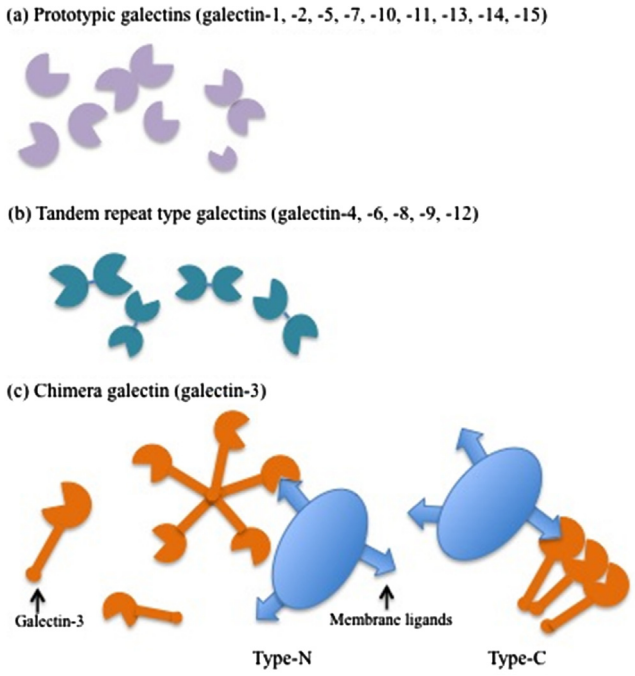

Fig. 1. The structure and classification of different members of the galectin family. Galectins are classified into three distinct subgroups based on the number and organization of their carbohydrate-recognition domain (CRD): a: prototypic galectins (galectin-1, -2, -5, -7, -10, -11, -13, -14, and -15) contain one CRD able to homodimerize; b: tandem repeat type galectins (galectin-4, -6, -8, -9 and -12) consist of a single polypeptide containing two distinct but homologous CRDs, separated by a linker of 70 amino acids; c: gal-3 is the unique chimera type. In addition to this lectinic dependent recognition, gal-3 can multimerize via its N-terminal domain (type-N self-association) or its CRD (type-C self-association).
Adapted from Blidner et al., 2013 [25] and Lepur et al., 2012 [19].

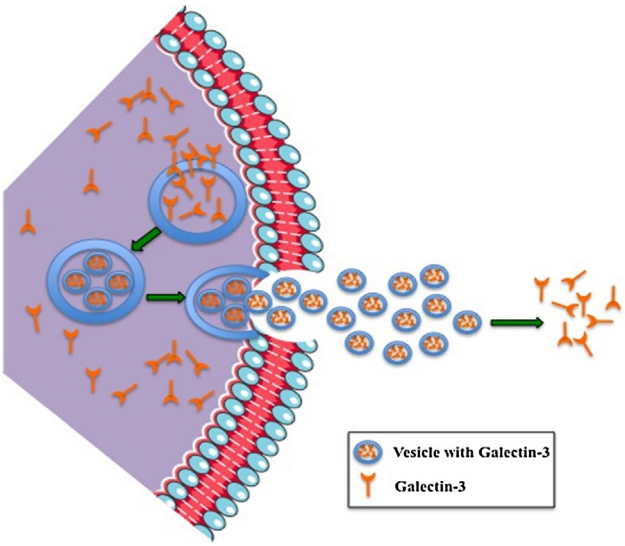

Fig. 2. The details of galectin-3 secretion. To be secreted, galectin-3 accumulates in the cytoplasm underlying plasma membrane domains. These aggregates evaginate and merge with the plasma membrane to form a protrusion that pinch off to release extracellular vesicles from which soluble lectin is released.
Adapted from Hughes, 1999 [15].

2.1. Galectin-3 synthesis and release

The gene coding gal-3 has been mapped on human chromosome 14 (14q21-22) and named *LGALS3* [13]. The protein is composed of three structural motifs including a short amino-terminal region of 12 amino acids, a collagenase-sensitive sequence rich in G-X-Y tandem repeats that are typical of the collagen supergene family, and a carboxy-terminal moiety containing the globular CRD.

Though gal-3 lacks a signal peptide, it can be secreted via a non-classic pathway called ectocytosis [14]. In this peculiar secretion pathway, cytosolic gal-3 accumulates under the plasma membrane and constitutes aggregates that are first included in evaginating protrusions (blebs) of the membrane. Then, these blebs release the soluble gal-3 into the extracellular space (Fig. 2). The secretion of gal-3 depends on cell types and could be facilitated by its interaction with membrane lipids in an energy-independent manner [15]. In non-polarized cells, gal-3 is transported through acidified endosomal compartments bound to vesicular carriers [16]. Whatever the secretion type is, residues 89 to 96 of the N-terminal domain containing proline are crucial [17].

2.2. Galectin-3 binding properties

Most functions of gal-3 are supported by its CRD, which binds to glycosylated structures. The affinity of galectins increases if galactose is linked to other carbohydrates and glycosylated structures containing N-acetyllactosamine residues are preferential ligands of gal-3 [18]. In addition to this lectinic C-terminal-dependent recognition, gal-3 must multimerize via its N-terminal domain (type-N self-association) to generate biological activities. However, a proteolytic cleavage of gal-3 in the intermediate collagen-like domain increases its binding affinity for the ligands although it does not induce any cell response. Few years ago, a Swedish group demonstrated that whole gal-3 could alternatively multimerize via the CRD, which also resulted in an increased affinity for the ligands.