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Importance of synovitis in osteoarthritis: Evidence for the use of glycosaminoglycans against synovial inflammation

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ABSTRACT

Objectives: After detailing the different aspects of synovial inflammation (i.e., cellular, biochemical, and vascular) and based on the current knowledge, the aim of this review was to collect the available in vitro and in vivo data regarding the potency of some glycosaminoglycan (GAG) compounds to target synovial inflammation, an important aspect of osteoarthritis.
Methods: The first part of the review corresponds to a qualitative review of the inflammatory status of OA synovial membrane. The second part corresponds to a systematic review of the literature regarding the potential effects of some GAGs on the previously described phenomenon.
Results: The synovial aspect of the inflammatory status of OA has been detailed. Chondroitin sulfate has demonstrated to control the three aspects of synovial membrane inflammation: cell infiltration and activity, biochemical mediators release, and angiogenesis. Glucosamine is also active on both cellular and molecular aspects of the inflammatory reaction. Hyaluronic acid seems to be anti-inflammatory in its native form, while products of degradation are reported to be pro-angiogenic.
Conclusion: Much evidence suggests that some of the studied GAG compounds could target different aspects of synovitis. Some of them could be considered in combination therapy since they exhibit complementary properties. Most of the studies have concentrated on articular cartilage and chondrocytes. In order to achieve a structure modification, one may now consider all joint tissues and investigate the drug potency on all of them. Potent treatment should trigger the most important features of OA: cartilage degradation, subchondral bone sclerosis, and all aspects of synovial inflammation.

Introduction

Osteoarthritis (OA), one of the most disabling arthritic affection, is now clearly defined as the disease of an organ, the joint [1]. It is acknowledged that cartilage is not the sole tissue affected by OA, but that the subchondral bone and the synovial membrane (SM) undergo metabolic and structural modifications related to the disease [2]. SM is indeed the scene of inflammation, resulting in joint swelling due to effusion in the joint cavity and stiffness [3,4]. Synovitis has been shown to be correlated with the severity and the progression of the disease [5,6]. It is the main cause of pain in OA patients.

The main recommendations for the management of OA [7–12] consist in the control of symptoms, i.e., inflammation and pain. Synovitis is classically treated by the intra-articular injection of corticosteroids and oral or topical NSAIDS in order to relieve pain [13,14]. Some of the recommendations agree with the use of glycosaminoglycan (GAG) compounds like chondroitin sulfate (CS), glucosamine (GlcN) sulfate, and hyaluronic acid (HA) [7,8,10–12]. They are characterized by a delayed, but significant effect on pain and function in knee OA. GlcN and CS have also been described with disease-modifying effects in knee OA.

Based on the current knowledge of the different aspects of synovial inflammation in OA, this review documents how selected GAGs, i.e., chondroitin sulfate, glucosamine, and hyaluronic acid could be potent interventions against synovitis in OA.

Methods

The first part of the review corresponds to a qualitative review of the inflammatory status of OA and synovitis. A search was performed on PubMed in order to provide an overview of this

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aspect of OA. The used keywords were “osteoarthritis” and “inflammation” or “synovitis” or “synovial inflammation.”

The second part of the review corresponds to a systematic review of the literature regarding the potential effects of the most studied GAGs on the previously described phenomenon. A thorough search has been performed on PubMed through March 2013 using the following keywords: “osteoarthritis,” “arthritis”; “synovial,” “synoviocytes”; “synovial fibroblasts”; “synovitis” or “inflammation”; “chondroitin”; “glucosamine”; “hyaluronic acid,” “hyaluronate” or “hyaluronan” or “glycosaminoglycans.” The inclusion criteria for this search were the following: in vitro and in vivo evidences related to inflammation and synovial tissues; results directly linked to OA (in vivo or in vitro and ex vivo); results obtained in related models (i.e., arthritis); results obtained in synovial tissue, synovial cells, and/or inflammatory cells; results with a direct link to the events described in the first part of the review; and only articles in English language. The exclusion criteria were the following: results reported in other inflammatory conditions, results with no direct link to inflammation, results obtained in other OA tissues (i.e., cartilage and subchondral bone), results obtained in other cell types than the included ones, and results obtained with other compounds than with the specified ones.

Results

Overview of the current knowledge on OA inflammation and synovitis

The inflammatory status of OA remained controversial for a long time. There was indeed no sign of systemic manifestation, and neutrophils in the synovial fluid of OA patients were way less important than in gout or rheumatoid arthritis (RA). However, inflammation in OA includes local inflammation that has been described in both early and late stages [15]. The inflammatory status in OA patients is undoubtedly less important than in RA patients but it is different from normal SM [15]. The importance of synovitis in OA has been largely reported. The use of new imaging techniques such as ultrasound (US), magnetic resonance imaging (MRI), or scintigraphy has revealed the high prevalence of synovitis in OA. Thus, synovitis was found in 95% of OA patients with effusion and also in 70% of patients without effusion [16]. Furthermore, synovitis is an indicator of pathology and a predictor of disease progression [17]. The prevalence and the severity of synovitis increase with advancing stage of OA.

The origin of synovitis [18,19] is strongly related to cartilage and meniscus degradation [20]. It is described as part of a vicious circle perpetuating OA. In addition, synovial tissue could contribute to the bone remodeling observed in OA by the differentiation of synovial macrophages into functional osteoclasts [21,22]. Taken together, these evidences position the SM at the center of the OA pathophysiological process and reveal the potential target, i.e., synovial inflammation for OA treatment. It would target both symptoms and structure modifications.

Synovial inflammation is classically revealed by histology. It is characterized by synovial thickening (hypertrophy and hyperplasia), cell infiltrate (macrophages and lymphocytes infiltration), and angiogenesis. These events imply the involvement of various mediators (inflammatory, immune, etc.) (Fig. 1).

Cellular aspect of synovitis

The increased number of lining cells consists in synovial layers made of synovial fibroblasts and in a mixed inflammatory infiltrate containing macrophages, T cells, and B cells [23–27]. Macrophages drive inflammation and destructive response. They are responsible for the production of the major inflammatory mediators [25]. They are also involved in osteophytes formation and synovial fibrosis through, at least partially, the local secretion of TGF-β [28]. Higher levels of mononuclear cell infiltration are found in synovial tissue of early OA patients than of late OA patients [26].

Innate immunity has been described as an early event of the OA synovitis [29,30]. The T cell infiltrate in OA SM is the site of Th1 differentiation and activation to produce Th1 cytokines, such as interferon γ (IFNγ) [31]. The local chronic T cell activation results in an angiogenic organization, especially in the perivascular areas [31] (Fig. 1). They express both leukocyte and endothelial adhesion

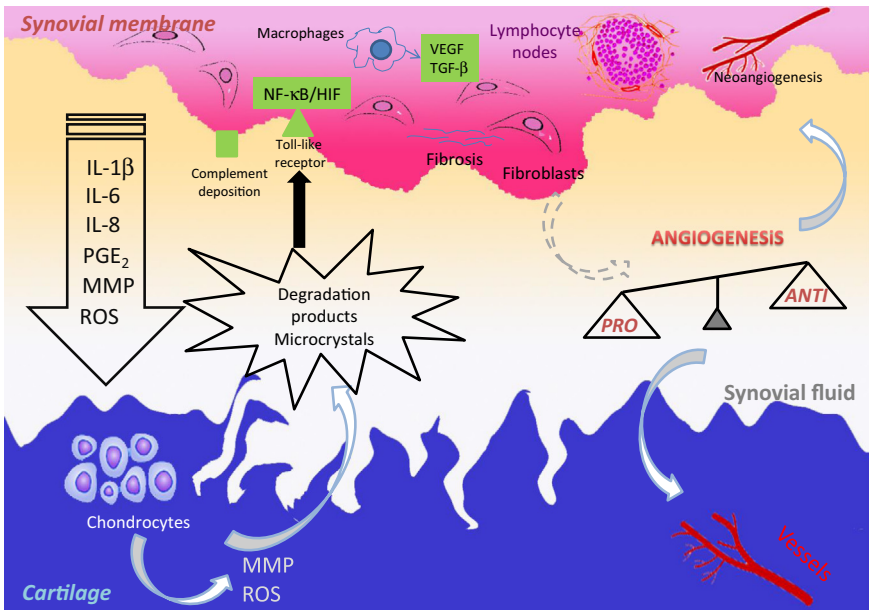

Fig. 1. The complex interaction between articular cartilage and synovial membrane during OA. The degradation products and microcrystals generated by cartilage activate the synovial membrane. In turn, it produces pro-inflammatory cytokines (IL-1β and TNFα), prostanoids, reactive oxygen species (ROS), and matrix metalloproteinase (MMP) that are freed in the synovial fluid and activate and contribute to cartilage degradation. The Toll-like receptors (TLR) present at the surface of synovial cells are activated and the complement is requested. The production of angiogenic factors is imbalanced in favor of the pro-angiogenic ones, resulting in the development of neo-vascularization in both cartilage and synovial membrane.