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Review

The joint synovium: A critical determinant of articular cartilage fate in inflammatory joint diseases

Pallavi Bhattaram*, Unnikrishnan Chandrasekharan*

Department of Cellular & Molecular Medicine, Cleveland Clinic Lerner Research Institute, 9500 Euclid Avenue, NC-10, Cleveland, OH, 44195, USA

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ABSTRACT

The synovium constitutes the envelope of articular joints and is a critical provider of synovial fluid components and articular cartilage nutrients. Its inflammation is a predominant feature and cause of joint degeneration in diseases as diverse as rheumatoid, psoriatic, juvenile and idiopathic arthritis, and lupus, gout and lyme disease. These inflammatory joint diseases (IJDs) are due to a wide variety of genetic, epigenetic and environmental factors that trigger, promote, and perpetuate joint destabilization. In spite of this variety of causes, IJDs share main pathological features, namely inflammation of the joint synovium (synovitis) and progressive degeneration of articular cartilage. In addition to being a driving force behind the destruction of articular cartilage in IJD, synovitis is also increasingly being recognized as a significant contributor of articular cartilage degeneration in osteoarthritis, a disease primarily due to aging- or trauma-related wear and tear of cartilage surfaces. In view of this important role of the synovium in determining the fate of articular cartilage, this review focuses on its underlying mechanisms in the pathology of IJD. We address the roles of synovial fibroblasts, macrophages and endothelial cells in the maintenance of joint health and in the destruction of articular cartilage integrity during IJD. Molecular mechanisms that have been recently shown to govern the pathological activities of the resident synovial cells are highlighted. Finally, advantages and disadvantages of targeting these new molecular mechanisms for preventing cartilage degeneration due to chronic inflammation are also discussed.

Contents

Abbreviations: EC, endothelial cells; FLS, fibroblast-like synoviocytes; IJD, inflammatory joint disease(s); OA, osteoarthritis; RA, rheumatoid arthritis; TNFα, tumor necrosis factor alpha.

* Corresponding authors.
E-mail addresses: bhattap2@ccf.org (P. Bhattaram), chandru@ccf.org (U. Chandrasekharan).

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1. Introduction

Synovium forms the boundary between the internal joint structures and the adjacent musculoskeletal tissues. It is organized into two distinct tissue layers: the synovial lining or intima, composed of 2–3 layers of fibroblast-like and macrophage-like synoviocytes, and the sub-intimal space, composed of fibrous connective tissue, blood vessels and a low content of immune cells (Fig. 1) [1,2]. Synovium is essential for joint homeostasis. It has fibroblast-like cells, which produce major constituents of the synovial fluid. Its vascular network provides nutrition to the avascular articular cartilage. It has macrophages that help in clearing bacterial infections and debris resulting from minor joint injuries from the synovial fluid. A small proportion of the synovial fibroblasts are believed to function as adult stem cells that may contribute to joint tissue renewal and repair [3]. As is the case with any tissue in the body, the synovium is frequently exposed to inflammation. Synovial inflammation, which is clinically described as synovitis, can result from physical trauma, bacterial and viral infections, joint wear and tear, and the presence of circulating autoantibodies. In most cases, the synovial cells promptly resolve inflammation. However, their failure to do so in specific cases results in the development of chronic inflammatory joint pathology, which may persist for lifetime (Fig. 1). The switch from a terminable inflammation to a persistent synovitis is thought to be the consequence of drastic behavioral changes occurring in the resident synovial cells. These changes epitomize many inflammatory joint diseases (IJD), including rheumatoid arthritis (RA), psoriatic arthritis, juvenile idiopathic arthritis and osteoarthritis (OA). Hyperplasia and increased vascularization of the synovium are followed by massive infiltration of T- and B-cells, plasma cells, and macrophages. Together, these new immune cells form a large mass of inflamed tissue called pannus. Products of inflammation emanating from this pannus destroy the adjacent articular cartilage matrix and subchondral bone [4–6].

Over the past decade, major advances have been made in the treatment of inflammation in IJD. Especially, the identification of the cytokines tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1) and IL-6 as major mediators of synovitis, and the introduction of TNFα inhibitors and other biological agents to target aberrant immune responses have greatly helped reduce chronic inflammation-induced joint structural damage and improve the quality of life of a large proportion of patients [7,8]. However, about 30% of RA patients experience lack of efficacy of anti-TNFα therapies or fail to maintain initial levels of response due to acquired drug resistance [9–11]. There are also concerns regarding the safety of prolonged use of TNFα inhibitors and other inflammation-targeting drugs as patients are at increased risk for developing infections. These problems demand an urgent need for the identification of alternate and more effective drug targets and treatment approaches. Research indicates that the synovium could provide the much-needed new therapeutic targets, since its resident cells are not just passive responders but are actually critical mediators of IJD progression [4–6]. Currently, significant research effort is directed towards understanding the physiology and molecular biology of synovial cells in health and disease. In this review, we first discuss the roles of resident fibroblasts, macrophages and endothelial cells in the maintenance of cartilage health. We succeed with a discussion on how transformation of synovial cells during IJD leads to articular cartilage degeneration. Finally, we speculate on potential therapeutic advantages of targeting the synovial cells to improving currently available treatments for IJD. We like here to note that non-resident immune cells also have important roles in the development of IJD, but we refer the readers to several recent review articles for information regarding these roles [12–14].

2. Roles of fibroblast-like synoviocytes in joint homeostasis

Fibroblast-like synoviocytes (FLS), also known as type-B synoviocytes or synovial fibroblasts, are specialized secretory fibroblast-like cells present in the synovial membrane and constituting up to 75% of all cells in the healthy synovium. FLS are interspersed with synovial macrophages, also known as type-A synoviocytes [1,2]. FLS express markers of the mesenchymal and fibroblast lineages, including vimentin, CD90 (Thy-1) and intracellular adhesion molecule 1. However, they can be distinguished from the sub-intimal and other types of fibroblasts based on higher levels of UDP-glucose-6-dehydrogenase, cadherin 11, receptor-type protein tyrosine-protein phosphatase sigma and vascular cell adhesion protein 1 [3,15,16]. The primary function of FLS in the maintenance of joint health is to control the composition of the synovial tissue extracellular matrix and synovial fluid. FLS secrete the proteoglycan lubricin, a major lubricant of the synovial fluid, and hyaluronic acid and heparan sulfate-linked proteoglycans, key constituents of the synovial tissue extracellular matrix. In addition, FLS have the potential to differentiate into chondrocytes in vitro and ex vivo and are thus being considered as an excellent cell source for tissue regeneration purposes in cartilage degenerative diseases [17,18].

3. Mechanisms governing cartilage degeneration by FLS

During IJD, especially rheumatoid arthritis, FLS transform from joint-protecting cells into joint-destroying cells. This pathological transformation is triggered by inflammation. Transformed FLS are often compared to cancer cells, as they escape apoptosis, proliferate rapidly, and produce growth factors and pro-angiogenic factors that increase the local vascular network. In addition, they are highly migratory. They attach to the articular cartilage, produce cartilage matrix-degrading enzymes, and once cartilage is eroded, they invade the underlying bone and activate osteoclast -mediated bone resorption. Furthermore, FLS produce chemokines and cytokines that attract a large number of immune cells into the synovium and also induce chondrocytes to secrete and activate extracellular matrix-degrading enzymes [4–6,15]. Multiple interdependent molecular mechanisms govern FLS transformation in response to inflammation. We highlight below key and newly discovered mechanisms that have great promise to be developed into therapeutic targets for preventing FLS-induced cartilage degeneration.

3.1. Activation of toll-like receptor signaling

A characteristic feature of FLS transformation is increased expression of toll-like receptors (TLR). These receptors can be activated by the binding of host-derived byproducts of injury and inflammation or exogenous products derived from bacterial and viral infections. Such molecules are abundant in the synovial fluid of patients with IJD (reviewed in [19]). The TLR pathway mediates its intracellular effects through the canonical NFκB, MAPK and IRF signaling cascades. Transcriptional targets of these cascades include the TLR receptors themselves as well as major