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REVIEW

Immunopathogenesis of osteoarthritis

Abdul Haseeb, Tariq M. Haqqi*

Department of Anatomy & Neurobiology, Northeast Ohio Medical University, 4209 St. Rt. 44, P.O. Box 95, Rootstown, OH 44272, USA

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Abstract Even though osteoarthritis (OA) is mainly considered as a degradative condition of the articular cartilage, there is increasing body of data demonstrating the involvement of all branches of the immune system. Genetic, metabolic or mechanical factors cause an initial injury to the cartilage resulting in release of several cartilage specific auto-antigens, which trigger the activation of immune response. Immune cells including T cells, B cells and macrophages infiltrate the joint tissues, cytokines and chemokines are released from different kinds of cells present in the joint, complement system is activated, and cartilage degrading factors such as matrix metalloproteinases (MMPs) and prostaglandin E_2 (PGE_2) are released, resulting in further damage to the articular cartilage. There is considerable success in the treatment of rheumatoid arthritis using anti-cytokine therapies. In OA, however, these therapies did not show much effect, highlighting more complex nature of pathogenesis of OA. This needs the development of more novel approaches to treat OA, which may include therapies that act on multiple targets. Plant natural products have this kind of property and may be considered for future drug development efforts. Here we reviewed the studies implicating different components of the immune system in the pathogenesis of OA.

Contents

* Corresponding author at: Department of Anatomy & Neurobiology, Northeast Ohio Medical University, F-144, 4209 St. Rt. 44, P.O. Box 95, Rootstown, OH 44272, USA.
E-mail address: thaqqi@neomed.edu (T.M. Haqqi).

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1. Introduction

Osteoarthritis (OA) is a chronic disease and results from damage to the articular cartilage induced by a complex interplay of genetic, metabolic, biochemical, and biomechanical factors followed by activation of inflammatory response involving the interaction of the cartilage, subchondral bone, and synovium [1]. Many factors—some modifiable—contribute to an increased risk of OA and include obesity, genetics, aging and trauma to the joint. In most patients without a strong genetic predisposition, OA is thought to start as a result of damage to the joint tissue by physical forces as a single event of trauma or by repeated microtrauma due to altered mechanical loading of the joint [2]. Chondrocytes respond to the physical injury by stopping the production of anabolic factors and by releasing more catabolic enzymes such as MMPs, which results in further damage to the cartilage [3], and this further leads to the release of matrix components, which elicit inflammatory mechanisms [4]. Involvement of an immune response, both innate and adaptive, in OA is now widely accepted based on the following evidence:

1) An inflammatory synovium/synovitis has been linked to increased cartilage damage [5] and pain [6] in recent epidemiological studies on large number of OA patients.
2) Infiltrates of immune cells including T-cells, B-cells and macrophages have been detected in synovial tissue of OA patients [7–9].
3) Immunoglobulins and immune complexes against cartilage components are detected in cartilage, synovium and plasma in OA patients [4].
4) Key role of complement activation in OA synovium has been identified [10].

Here we provide a review and recent updates on the involvement of major aspects of immune system, including innate and adaptive immune responses, in the pathogenesis of OA.

2. Innate immunity

2.1. Cellular factors: monocytes/macrophages and other cells of innate immunity in OA

Macrophages are among the most abundant cell types present in the cellular infiltrates found in the inflamed synovium in OA [7,11,12]. Macrophage-derived cytokines, including IL-1β and TNF-α are the major players in the cartilage breakdown in OA [discussed later in this review]. Several chemokines responsible for chemotaxis of macrophages have been implicated in the development of OA. Using a collagenase-induced mouse model it was shown that depletion of synovial macrophages by injection of clodronate-laden liposomes resulted in decreased TGF-β-induced osteophyte formation [13]. Using the same model Blom et al. showed that the activation of synovial macrophages is required for the production of MMPs and cartilage damage [14]. Bondeson et al. developed a macrophage depleted synovial cell culture model by using CD14-conjugated magnetic beads. Specific removal of synovial macrophages from these cultures resulted in significantly decreased production of cytokines, IL-1β and TNF-α, indicating that the sources of these cytokines were synovial macrophages. Further, macrophage depletion also resulted in decreased production of IL-6, IL-8, MMP-1 and MMP-3 [15].

Presence of natural killer cells was reported in synovial tissues obtained from patients undergoing total joint replacements, which constituted about 30% of the CD45+ mononuclear cell infiltrate [16]. These cells showed a quiescent phenotype consistent with post-activation exhaustion. Presence of low level of activated dendritic cells was also reported in OA synovium [17]. Recently, dendritic cell infiltrates were detected in the synovial tissue of rabbits with surgically induced OA in the early stages of the disease (2 and 4 weeks post-operation) [18]. However, the role of both NK cells and dendritic cells in OA pathogenesis has not yet been elucidated in detail.

2.2. Humoral factors

2.2.1. Activation of complement system in OA

The complement system constitutes a crucial effector mechanism in the immune system to clear the pathogens and immune complexes and consists of a cascade of very tightly regulated array of proteins, improper regulation of which may lead to self tissue damage. The deposition and activation of complement factors in OA cartilage have been documented in several early studies in OA patients as well as in animal models of OA [19–22]. Tarkowski et al. observed expression of decay accelerating factor (DAF) in the synovial lining cell layer both in rheumatoid arthritis (RA) and in osteoarthritis (OA) along with C5b-9 terminal complement complex suggesting an activation of complement-mediated response [23]. Corvetta et al. found a correlation of terminal complement complex deposits in synovial tissue with the extent of inflammatory synovitis, irrespective of whether the synovitis was in RA or OA patients [24]. Doherty et al. found C3 activation to be associated with RA and gout but