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Review

Current concepts in the pathogenesis of osteoarthritis

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Introduction

Osteoarthritis (OA) is a degenerative joint disease that progressively causes loss of joint function and is the leading source of physical disability and impaired quality of life in industrialized nations. The burden of disease dramatically impacts health care usage and leads to total joint replacement in approximately a half-million Americans alone each year – and such consequences on society worldwide are expected to rise in coming decades with the continued expanding and aging population.

There are no current interventions proven to restore cartilage or curtail the disease processes. Thus, OA often ultimately results in joint destruction, chronic pain, disability, depression and social isolation. Multiple etiologic risk factors and pathophysiologic processes all contribute to the progressive nature of the disease – and serve as targets of behavioral and pharmacologic interventions. Risk factors, such as age, gender, trauma, overuse, genetics and obesity each make contributions to initiate the process of injury in different components of the joint; then the effector biochemical processes involving the cartilage, bone, and synovium eventually intertwine and collectively damage all three components as well (Fig. 1)¹. These effects on the tissues of all three joint compartments manifest as articular cartilage breakdown, osteophyte formation, subchondral sclerosis, bone marrow lesions and alterations of the synovium on both morphologic and biochemical levels often causing episodic synovitis. Thus, the molecular and cytokine-based events that drive joint damage in inflammatory arthritides have gradually emerged as pathogenic paradigms in OA, and will be highly relevant to the development of future OA therapeutics. With increasing appreciation of the contribution of all three joint compartments to disease progression, current research in OA pathogenesis, biomarkers and treatment has broadened immensely in recent years. In this review, we will focus on emerging pathogenic concepts that will hopefully help advance the search for effective disease-modifying osteoarthritis drugs (DMOADs).

Cartilage: a target and a protagonist

The synovium, bone, and cartilage are each well established tissues impacted by the pathological mechanisms occurring in OA. Local and intertwined abnormalities in these compartments lead to progressive joint degeneration, yet the cartilage has traditionally received the most attention in the study of OA because of the gross damage found in pathology specimens and imaging studies, and the multitude of biochemical processes that are activated. Key events occurring in cartilage during the pathogenesis of OA include an imbalance of metabolic and degradative signals, driven by cytokine cascades and the production of inflammatory mediators. Chondrocytes, as well as synovial cells, of OA patients produce increased levels of inflammatory cytokines, such as interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α), which in turn decrease anabolic collagen synthesis and increase catabolic (including matrix metalloproteinases or MMPs) and other inflammatory mediators such as IL-8, IL-6, prostaglandin E2 and nitric oxide (NO)^{2,3}.

Coupled with the various activated degradative biochemical pathways are often biomechanical derangements, such as those seen in joint malalignment or obesity, which can both predispose to and perpetuate OA. It is clear that the altered biomechanics seen in OA induce and potentiate biochemical changes and it has been shown that both static and dynamic compression of cartilage explants tends to up-regulate many molecules such as aggrecan, fibronectin, MMPs, aggrecanase-2 (ADAMTS-5), and c-fos, c-jun^{4,5}. Therefore, gene expression by chondrocytes in cartilage after injurious compression mimics in some ways that observed after IL-1 β stimulation, and may offer an opportunity for pharmacological intervention. In addition, mechanical stress, by both static and intermittent compression, increases NO production by chondrocytes as well as nitric oxide synthase (NOS) expression. Therefore, *in vivo*, NO production may be in part regulated by biomechanics⁶. In turn, NO contributes to articular cartilage damage and plays multiple roles with respect to its effects on chondrocytes. Overall, it promotes cartilage degradation by inhibition of collagen and proteoglycan synthesis, MMP activation, and increased susceptibility to other oxidant injury.

Reactive oxygen species (ROS) have been implicated in directly promoting chondrocyte apoptosis, catabolic processes and matrix degradation. Thus two important pathogenic events characteristic of OA chondrocytes, premature senescence and apoptosis, appear to result

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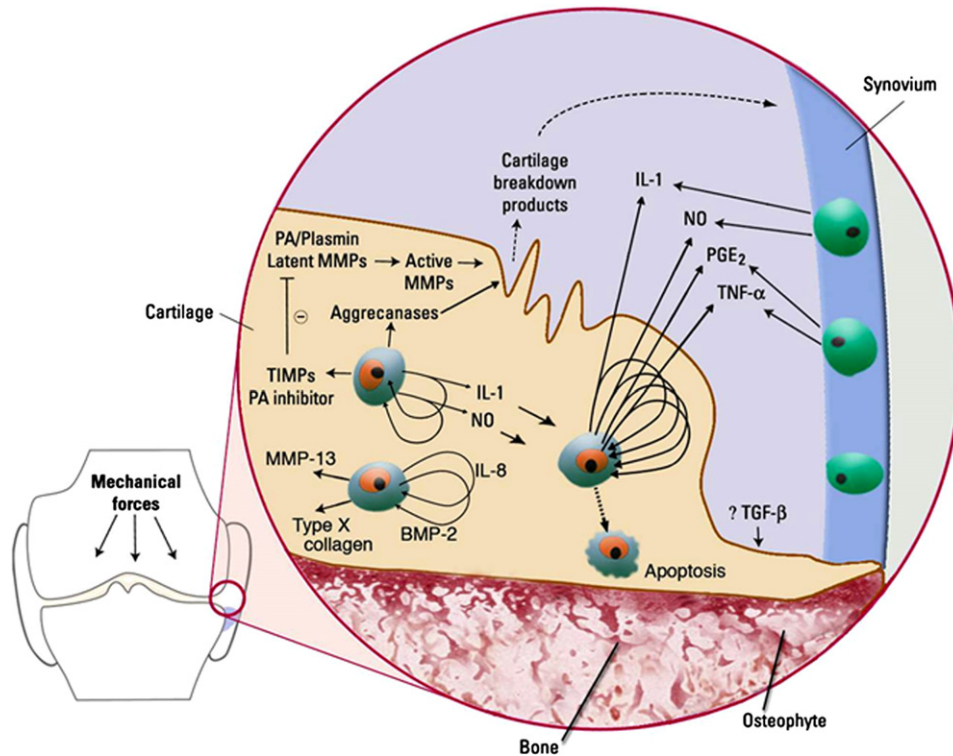


Fig. 1. Molecular pathogenesis of OA. Potential biomarkers and targets for disease modification are released as a result of events in cartilage, bone, and synovium. Figure adapted from Ref. 1.

from NO and other oxidative injury^{7–10}. These events help drive the concept that OA is a disease of premature aging of the joint. Senescence is characterized by shortened telomeres, increased levels of B-galactosidase and decreased ATP production from mitochondrial dysfunction¹¹. These changes have been demonstrated histologically in chondrocytes taken from OA patients¹². Studies suggest that the telomere shortening and reduced number and function of mitochondria seen in OA chondrocytes are results of oxidative stress. Other work implicates NO as an important mediator in chondrocyte apoptosis, which is a common feature in progressive OA. Immunohistochemistry of joint tissue from OA patients co-localizes apoptotic areas with iNOS protein

in articular cartilage cells¹³. The findings of premature senescence and apoptotic acceleration in OA substantiate that the disease is age dependent, mechanically driven, and chemically, particularly ROS-mediated.

Role of synovium

It is now widely accepted that not only is OA more than a disease of cartilage, but that it is a failure of the whole joint, which leads to and perpetuates the disease processes. The classification of OA as a non-inflammatory arthritis is in part due to the low synovial fluid leukocyte

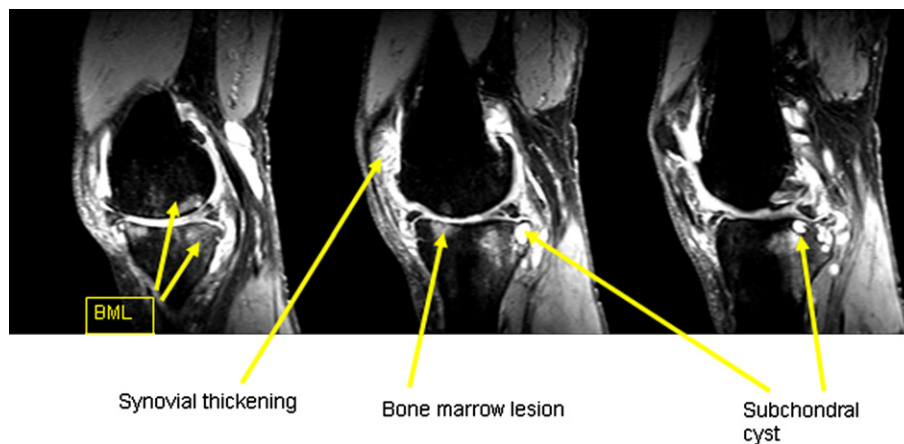


Fig. 2. Significant synovial thickening, bone marrow lesions and subchondral cysts.

counts, yet the clinical presentation (often with swelling, effusions, and stiffness) clearly reflects synovial inflammation, implicating it as a low-grade contributor in disease pathogenesis. Synovitis occurs even in early OA and can be sub-clinical, as arthroscopic studies suggest that localized proliferative and inflammatory changes of the synovium occur in up to 50% of OA patients — many of whom do not appear to have active inflammation¹⁴. Newer, more powerful imaging techniques using 3 T magnetic resonance imaging (MRI) scanning have also strengthened the concept that synovial inflammation is more common than may have been previously appreciated. Our recent work has revealed localized areas of synovitis, which may not be detectable either on physical exam or using other modalities such as ultrasound (Fig. 2). In addition, in a cross-sectional study, we found that increasing synovial volume, as detected on gadolinium-enhanced MRI, correlates with the severity of knee OA by KL score, as well as with joint space narrowing¹⁵. Synovial histological changes include synovial hypertrophy and hyperplasia with an increased number of lining cells, often accompanied by infiltration of the sublining tissue with scattered foci of lymphocytes. In contrast to rheumatoid arthritis (RA), synovial inflammation in OA is mostly confined to areas adjacent to pathologically damaged cartilage and bone. This activated synovium can release proteinases and cytokines that may accelerate destruction of nearby cartilage.

The synovium produces some of the chemokines and metalloproteinases that degrade cartilage, even though the cartilage itself produces most of these destructive molecules in a vicious autocrine and paracrine fashion. In turn, cartilage breakdown products, resulting from mechanical or enzymatic destruction, can provoke the release of collagenase and other hydrolytic enzymes from synovial cells and lead to vascular hyperplasia in OA synovial membranes. Generally, inflammation and angiogenesis often accompany each other, and this seems to be no different in the OA joint, where inflammation facilitates angiogenesis and angiogenesis then potentiates inflammation. Inflammatory cells such as macrophages not only secrete pro-angiogenic factors, but also secrete factors that stimulate other cells, such as endothelial cells and fibroblasts, to produce vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and other factors that further promote angiogenesis. Then, the blood vessel permeability and up-regulation of adhesion molecules that are seen as part of angiogenesis perpetuates the inflammatory response. Additionally, a new road map is created to continue to transport these inflammatory cells and nutrients to the sites of inflammation¹⁶.

OA is by far the most common type of arthritis encountered worldwide, yet the development of effective disease-modifying treatments continues to lag behind that of the inflammatory arthritides. Current goals that are still to be

achieved include understanding better how the numerous multi-factorial forces (e.g., genetic, biomechanical, hormonal, etc.) converge to manifest the OA phenotype and improving identification of patients at risk of clinically meaningful progression, by using growing knowledge of the epidemiological, genetic, biochemical and imaging findings, perhaps even in a combinatorial manner. As the pathogenesis of OA is further elucidated, and the discovery of improved biomarkers continues, we hope to see true DMOADs emerge in the near future.

Conflict of interest

The authors have no conflict of interest.

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