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Inflammation and Cartilage Degradation in the Pathophysiology of Osteoarthritis: Potential for Targeted Therapies

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Abstract

Generally, osteoarthritis (OA) is considered to be a common degenerative joint disorder characterized by destruction of the articular cartilage, subchondral bone alterations and low-grade joint synovitis. Aging population and obesity are increasingly being associated with a concomitant increase in the incidence of OA and disability worldwide causing significant burden on the individual and society. The understanding of OA has evolved over years from a degenerative (wear and tear) non-inflammatory disease to a disease of joints that results from many predisposing factors including: aging, genetics, excessive exercise, obesity, genetic predisposition, inflammatory autoimmune disorders, poor nutrition, injury, metabolic disorders such diabetes mellitus, homocysteinaemia, joint trauma, hormonal imbalance, altered biomechanics, obesity and infection. All these factors contribute to an imbalance between catabolism and anabolism of joint cartilage leading to eventual joint damage and structural joint failure. This review focuses on the pathophysiological basis of OA highlighting the potential of specific targeted treatments.

Keywords: Osteoarthritis; Pathophysiology; OA treatment; Cytokines; Inflammation; Targeted therapy

Abbreviations: OA: Osteoarthritis; RMD: Rheumatic and Musculoskeletal Disease; DMOADs: Develop Disease Modifying Osteoarthritic Drugs; AGE: Advanced Glycation End Products; MMPs: Metalloproteinases; VIP: Vasoactive Intestinal Peptide; BMI: Body Mass Index; CGRP: Calcitonin Gene Related Peptide; IGF-1: Insulin-like Growth Factor 1; NO: Nitric Oxide; PGE2: Prostaglandin E2; ECM: Extra-Cellular Matrix; mPGES-1: microsomal PGE Synthetase-1; sPLA2: soluble Phospholipase A2; IFNY: Interferon Gamma; COX2: Cyclo-Oxygenase 2; BMLs: Bone Marrow Lesions

Introduction

Osteoarthritis (OA) is one of the most common non-inflammatory rheumatic and musculoskeletal disease {RMD} associated with progressive cartilage destruction which leads to structural and functional joint failure. Aging and other concomitant diseases such as diabetes mellitus are associated with significant increased risk of developing OA. The understanding of OA has evolved over years from that of a degenerative (wear and tear) non-inflammatory disorder to a disease of joints that results from many predisposing factors that include inter alia: aging, genetic predisposition, excessive exercise, obesity, genetic predisposition, hormonal imbalance, inflammatory autoimmune disorders, poor nutrition, injury, metabolic disorders such diabetes mellitus, homocysteinaemia, joint trauma, altered biomechanics, obesity and infection [1-3].

Despite OA being the most common joint disease, there is still is no definitive or preventive treatment other than symptomatic treatment. As the aging population increases globally, OA poses a significant financial and social burden. This highlights the need to develop disease modifying osteoarthritic drugs (DMOADs) [2]. A full understanding of the pathophysiologic and inflammatory pathways that initiate the onset and progression of OA will facilitate the development of targeted therapies [2,3]. Early diagnosis as well as understanding the risk factors and development of biomarkers of OA will aid early therapeutic intervention. The pathophysiologic mechanisms involved in OA are complex and multiple, and lead to the development of a state of chronic inflammation resulting in propagation and progression toward the phenotype of clinical OA [3]. Current studies have shown that inflammatory cytokines

produced also by chondrocytes, induce chondrocytes to release metalloproteinases that degrade cartilage [4]. This review will focus on the pathophysiological basis of OA highlighting the potential of targeted treatments and need to continue to design such strategies.

Pathophysiology

Chondrocytes produce articular cartilage. Cartilage is comprised of extracellular collagen matrix and various proteoglycans. Cartilage is metabolically active and is constantly renewed throughout life [1-5]. The elasticity and compressibility of cartilage is due to the proteoglycan Aggrecan. Aggrecan is a central core protein comprising of numerous glycosaminoglycan chains of chondroitin sulphate and keratan sulphate moiety which are attached to hyaluronic acid [5]. The collagen functional and metabolic network is disrupted with ageing leading to fissuring and increased levels of advanced glycation end products (AGE). AGE binds specific advanced glycation end products (RAGE) receptors found on the surface of chondrocytes. This binding perturbates the catabolic activity in chondrocytes [6]. AGEs can also induce oxidative stress in cells triggering the secretion of many pro-inflammatory cytokines and chemokines.

A variety of cellular factors involved in the pathogenesis of OA are inter alia: mononuclear cells, chondrocytes, osteoblasts and osteocytes, and synovial lining cells [1-19]. A variety of soluble mediators such as: proinflammatory cytokines {tumour necrosis factor α (TNFα), interleukin 1β (IL-1 β), interleukin 6 (IL-6)}, transforming growth factor β (TGF β), metalloproteinases (MMPs), lipid mediators [Prostaglandin E2 (PGE2)], nitric oxide (NO), insulin-like growth factor1 (IGF-1), adipokines (leptin, adiponectin, resistin) and neuropeptides [neuropeptide Y, vasoactive intestinal peptide (VIP), substance P, and calcitonin gene related peptide (CGRP)] are also involved in the disease pathophysiology [2,7,8]. Neuropeptides induce pain in OA via afferent sensory nerve nociceptors which signal to the brain the via the spinal and spinothalamic tracts [9]. Nociceptors are found on several structures of the osteoarthritic joint such as the synovium, periosteum, subchondral bone and ligaments [7,8].

Chondrocytes express estrogen receptors which can mediate the production of growth factors [7]. The synthesis of these growth factors is decreased in menopausal women due to a reduction in estrogens [7]. One of the risk factors for OA in weight-bearing joints and also for non-weight-bearing joints such as hands is obesity. Adiposity contributes to a proinflammatory milieu since adipose tissue secretes many inflammatory mediators such as adipokines and leptin [10,13]. Leptin is also found in osteophytes and cartilage from patients with OA and its levels in synovial fluid correlate with body mass index (BMI). Leptin is pro-inflammatory and stimulates the synthesis of IGF-1 and TGFβ, and proteoglycans by chondrocytes [11,12]. Leptin enhances the capacity of pro-inflammatory cytokines to induce NO synthesis [12,24]. Visfatin is one of the adipokines which has been shown to enhance cartilage degradation [13]. Adiponectin levels are low in obese patients and are also negatively associated with hand OA progression [14].

Pro-inflammatory cytokines can activate chondrocytes, synovial cells and osteoblasts. OA Chondrocytes from OA patients can secrete a number of metalloproteinase enzymes such as MMP-1 (collagenase 1), MMP-3, MMP-9, MMP-13 (collagenase 3), aggrecanase, ADAMTS-4 and ADAMTS-5, that all degrade cartillage. Specific endogenous metalloproteinase tissue inhibitors (TIMPs) {TIMP1, TIMP2, TIMP3 and TIMP4} are also produced and inhibit MMPs activity. is determined by The MMPs and TIMPs balance ratio, determines the rate of cartilage matrix degradation in joints. Collagenase 1 and 3, and MMP-13 (collagenase 3) can cleave type II collagen [5]. Cartilage degradation can also be induced by Stromelysin-1 (MMP-3), Stromelysin-2 (MMP-10), Stromelysin-3 (MMP-11) [15]. Matrisylin (MMP-7) also plays a role in the degradation of proteoglycans [16]. IL-1β differential regulates MMPs and TIMP syntheses suggesting that the low the grade IL-1β production in joints may promote cartilage degradation by relative upregulation of MMPs versus TIMP, thereby creating an unfavorable balance between the level of the degrading enzymes and their inhibitors [17].

Abnormal mechanical forces and oxidative stress can stimulate chondrocytes, synovial cells and subchondral osteoblasts to produce proinflammatory cytokines {IL-1β, TNF-α} [18]. These cytokines can initiate a variety of catabolic and degradative processes in cartilage mediated by metalloproteinases that degrade cartilage extra-cellular matrix (ECM) [2,19]. The expression of ADAMTS-4 and ADAMTS-5 and enhanced production PGE2 can be induced by IL-1β and TNF-α via enhanced of the gene expression and/or activities of COX-2, microsomal PGE synthetase-1 (mPGES-1), and soluble phospholipase A2 (sPLA2). IL-1β and TNF-α can also stimulate nitric oxide synthetase (iNOS or NOS2) to upregulate NO production and stimulate other production of other proinflammatory cytokines such as IL-6, LIF (leucocyte inhibiting factor), IL-17 and IL-18, chemokines and IL-8. Serum levels of IL-6 and IL-8 are significantly higher OA patients when compared to healthy subjects. The genes associated with the differentiated chondrocyte phenotype, including aggrecan (AGAN) and type II collagen (COL2A1) are suppressed by IL-1β and TNF-α [5]. The inhibition of IL- 1β involves upregulation of: IL-1 Receptor antagonist (IL-1Ra), soluble form of IL-1R, and anti-inflammatory cytokines [2,20]. On the other hand, the anti-inflammatory cytokines IL1Ra, IL-4, IL-10, IL-13 and interferon gamma (IFNY) are also present in the OA joint. They inhibit the secretion of some MMPs and may differentially increase the synthesis of TIMPs [21]. Defective production of these anti-inflammatory factors could contribute to OA pathogenesis.

IL-1β and TNF-α, and lipopolysaccharides {produced by bacterial infections}, can upregulate iNOS gene expression and induces NO production. In chondrocytes. NO is involved in the degradation of cartilage by down-regulating the synthesis of IL-

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1Ra, aggrecan and collagen, enhancing MMPs activity. NO may contribute to chondrocyte apoptotic cell death by downregulating cell survival signals from the ECM [22,23]. In experimental animal models of OA, inhibitors of NO synthesis retard the development of histological changes and clinical features of experimental OA [24]. The eicosanoid pathway is also involved in chondrocyte activation [25,26]. Pro-inflammatory cytokines induce Prostaglandin E2 (PGE2), via the PLA2 pathway, cyclo-oxygenase 2 (COX2) and mPGES1. The activity of synovial cells, macrophages, chondrocytes is modulated by PGE2, which also induces bone resorption [27]. PGE2 induces several MMPs and can potentiate the action of other inflammatory mediators.

A loss of chondrocyte maturational arrest which pushes chondrocytes towards a more differentiated, hypertrophic-like state, has been observed in cartilage from OA patients. This chondrocyte hypertrophy increases the expression of type X collagen, upregulation of matrix metalloproteinases-13 and induces the synthesis of type II collagen and aggrecan, (MMP-13), synthesis of shorter proteoglycans and initiation of pathological calcification [27]. Chondrocytes can also interestingly, acquire a de-differentiated phenotype associated with increased types I and III collagen synthesis whilst type II collagen synthesis is inhibited [27]. Chondrocytes also acquire an activated phenotype corresponding to a pro-degradative state producing several proteinases induced prostaglandins), free radicals (NO, H_2O_2) and cytokines. These mediators perpetuate chondrocyte activation creating a vicious loop for cartilage degradation. NO induces NF-κB signaling that enhances pro-inflammatory cytokine production in the joint. NO also induces apoptotic chondrocyte cell death which further could decreases the synthesis of ECM components [21].

Cartilage breakdown products also enhance synovial inflammation which enhances catabolic and pro-inflammatory processes leading to excessive production of metalloproteinases that also break cartilage matrix establishing a positive feedback loop. The synovial tissue from OA joints is infiltrated with macrophages and T cells associated with enhanced inflammatory cytokine expression in both early and late OA. Another important feature of OA pathophysiology is also the presence of sclerosis, osteophytes, bone cysts and bone marrow lesions (BMLs) and subchondral bone remodeling [28]. BMLs can occur at the onset of the disease and are now considered to be a precursor for OA development as well [29,30]. Osteoarthritis subchondral osteoblasts can stimulate overproduction of IL-6, IL-8, C-terminal type I procollagen propeptide, alkaline phosphate, osteocalcin, TGF β1, IGF-1, urokinase, and osteopontin [28-31]. These osteoblasts in the affected joints, fail to respond to the bioactivity of parathyroid hormone, which might explain the dysregulated bone remodeling and osteophyte development [28].

Stimulation of trans-membrane G protein–coupled receptors by a variety of stimuli such as cytokines, hormones, neurotransmitters inter alia, initiates intracellular signaling by recruitment of by recruiting of the G protein-coupled receptor kinase 2 (GRK2). Perturbations of the GRK2 molecular pathway may also be involved in OA pathophysiology. GRK2 is involved in myocardial cell hypertrophy. Its expression has also been found to be increase in the chondrocytes from mouse models of OA and injured human cartilage and may also be involved in chondrocyte hypertrophy [31]. It has been observed that gene deletion of GRK2 in mice decreased experimental OA development [32]. This suggests a potential important role of GRK2 in OA pathophysiology. Finally, subchondral bone is involved in the pathogenesis of OA. Firstly, mechanical stress induce osteoblasts to produce the degradative MMP-1, MMP-13, PGE2 and IL-6. Secondly, enhanced expression of IGF-1 and TGF β in subchondral bone initiates new bone formation and development of osteophytes and subchondral sclerosis.

In conclusion, OA) is now considered to be a slow progressive inflammatory disease characterized by low grade inflammation, degradation of articular cartilage and joint function failure and pain. The balance between catabolic and anabolic mediators and their regulators is dysregulated. In addition, cartilage, the pathophysiologic processes also involve the entire joint, with active participation by subchondral bone, ligaments, capsule, synovial membrane and periarticular muscles. The understanding of the molecular and cellular pathophysiology of the disease is opening up novel therapeutic options using existing treatment modalities and potential to design and develop new ones.

Novel Therapeutic Approaches

The classical mode for the management of OA has been control of symptoms with a variety of symptom modifying OA drugs (SMOAD). The understanding of the pathophysiology of OA has given hope to the potential of disease modifying OA drugs (DMOAD) that are expected to modify the underlying OA pathophysiology, thereby inhibiting structural damage to prevent and/or reduce the development of mechanical joint failure and associated disability, and provide symptomatic relief of pain as well as mitigate the need for surgery. A number of targets have been identified for target therapy approaches:

Targeting Inflammatory sites

a. IL-1 inhibition

i. Anakinra

ii. Canakinumab

iii. Gevokizumab

iv. Lutikizumab

Targeting Bone Marrow Lesions

a. Bisphosphonates

b. Strontiun ranelate

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c. Teripatide

d. Vid D3

e. Calcitonin

Targeting Cartilage Metabolic pathway

a. Growth factors

b. Wnt signaling pathway

c. Cathepsin-K

d. MMP/ADAMTS

e. AMPK pathway

Pain Mechanisms

a. NGF

b. Intra-articular corticosteroid injections

A number of trials have been helping with existing drugs with mixed results and outcomes [33-44]. A number of challenges are there. The existing drugs have an unfavorable safety profile given the nature of OA. There is therefore an unmet medical need for DMOADs which would be expected to bring significant clinical effects to OA management in the future. However, since catabolic and proinflammatory mediators (intracellular signaling, cytokines, GRP2, nitric oxide, neuropeptides prostaglandins) are involved in perturbating balance between cartilage matrix production, degradation and repair as well as OA synovitis, there is a potential for targeted therapeutic management.

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