Osteoarthritis

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Osteoarthritis (OA) is a most common type of arthritis occur in the aged population. It affects any joint in the body and degenerates the articular cartilage and subchondral bone. Despite the pathophysiology of OA is different, still cartilage resorption is a symbol of osteoarthritis. Matrix metalloproteinases (MMPs) are important proteolytic enzymes that degrade extra-cellular matrix proteins (ECM) in the body. MMPs contribute to the turnover of cartilage and its break down; their levels have increased in the joint tissues of OA patients. Application of chondroprotective drugs neutralize the activities of MMPs. Natural products derived from herbs and plants developed as traditional medicine have paid much attention due to their potential biological effects. Therapeutic value of natural products in OA has increased reputation by presenting clinical impact with insignificant side effects. Several MMPs inhibitor have been used as therapeutic drugs for long time. Recently, different types of compounds have been reviewed for their biological activities. In this review, we summarize numerous natural products for the development as MMPs inhibitors in arthritic diseases and describe the major signaling targets that involved for the treatments of these destructive joint diseases.

Keywords: arthritis ; MMPs ; natural products ; chondroprotection ; signaling pathways

1. Introduction

Osteoarthritis (OA) is the most common type of joint disease that affect millions of people worldwide and it primarily cause disability in the aged population, affecting about 80% of individuals over the age of 75 [1]. Increased damage of cartilage degradation is the hallmark of this destructive joint disease. In the cartilage matrix, proteoglycan and collagen exist as major elements, and damage of proteoglycan could induce cartilage degeneration [2], followed by the catabolism of collagen fibrils, which increases the loss of cartilage structural integrity [3]. Matrix metalloproteinases (MMPs)-induced cartilage degeneration is controlled by endogenous tissue inhibitors of metalloproteinase (TIMPs) [4], and the disproportion in the ratio of TIMPs and MMPs could lead to a persistent matrix destruction in OA [5]. It was proposed that MMPs inhibition should be considered a therapeutic strategy in preventing cartilage degradation, which occurs in the arthritic process [6]. Although several inhibitors of the MMPs have been proposed as important therapeutic agents, there is a lack of evidence related to the inhibition of MMPs by natural compounds for chondroprotection in the destructive joint diseases.

2. MMPs and Osteoarthritis

Matrix metalloproteinases are proteolytic enzymes that restore and degrade extracellular matrix (ECM) proteins and their components. MMPs enzymes break down cartilages and their levels are elevated in joint tissues of patients with rheumatoid arthritis (RA) and OA [7]. Joint inflammation and joint degenerative diseases are associated with increased level of MMPs; so far, 23 MMP proteins have identified in humans [8]. Chondrocytes are vital cells that exist in the cartilage and are mostly accountable for affecting ECM in joint space. Chondrocytes synthesize collagen type II and aggrecan, which are similar to ECM and secrete proteolytic MMPs.

Collagenases, such as MMP-1 and 13 are highly degraded collagens in the cartilage and bone. In osteoarthritis, the components of cartilage matrix are hydrolyzed quickly and results in cartilage degradation. Collagenase-1 (MMP1) exists in various cells, including chondrocytes [9]. MMP13 (collagenase-3) majorly induce collagen degrading activity, especially of type II collagen [10], and this enzyme plays a major role in the degradation of cartilage. Various MMP inhibitors were established and verified for potential clinical use [11]. Moreover, MMP-13 expression co-express with CII degradation in OA lesions, indicating that this enzyme exerts a pivotal role in cartilage degradation in OA [12]. Moreover, immunohistochemistry has revealed the presence of MMP13-specific type II collagen degradation products and MMP13 enzymes in OA cartilage [13][14]. Though MMPs1, 8, and 13 have reported the only mammalian enzymes that degrade native fibrillary collagen types I, II, and III, other MMPs, including MMP2 and MMP14 also possess this activity [15][16]. The collagenases enzyme MMP2 and MMP9 degrade type IV collagen, gelatin, and elastin, which are complicated in joint diseases [17].

3. Inflammatory Cytokines in Osteoarthritic Chondrocytes

Inflammatory cytokines are the most important class of compounds contributing to the pathogenesis of OA. In the cartilages, interleukin-1β (IL-1) and tumor necrosis factor-α (TNF) were shown to induce of MMPs 1, 3, 9, and 13 expression [18], and these cytokines are found to be a suitable model in the human SW1353 chondrosarcoma cell line that is compatible with primary chondrocytes in OA [19]. Interleukin-1β stimulates the release of degenerative MMPs enzymes from chondrocytes and synoviocytes, and extracellular matrix proteins in chondrocytes [20]. IL-1β is also involved in the osteoclastogenesis and bone resorption, which is augmented in rheumatoid arthritis (RA) joints [21]. Apoptotic chondrocyte death in articular cartilage was observed in clinical specimens from RA and OA cartilages [22]. A previous study reported that anti-TNF-α treatment with a TNF antibody, gives a continued reduction of pain symptoms in OA [23], therefore, antagonists to TNF-α might serve as a potential beneficial strategy to decrease OA pain in patients [24].

Interleukin (IL)-1 is one of the most essential degrading cytokines secreted by chondrocytes in arthritic joint disease [25]. Augmented levels of IL-1 were noticed in synovial fluids from RA and OA patients [26], and its over expression in osteoarthritic cartilage tissue was also reported by Teslow et al. [13]. A high level of IL-1 receptor type 16 was observed in osteoarthritic chondrocytes, compared to normal chondrocytes, and inhibitors of IL-1 converting enzyme, a protease crucial for IL-1β processing, was found to reduce collagen-induced arthritis [27]. Moreover, opposing data were noted in a potential up- and down-regulation of IL-1β, in osteoarthritic cartilage [28]. IL-1 was reported to produce excessive effects in chondrocytes, including (i) a major reduction in the expression of collagen type II [29]; (ii) over expression of MMP-1, 3, and 13 [30]; and (iii) solid stimulation of intercellular mediators like leukemia inhibitory factor and IL-6. Interleukin-6, another well-recognized cytokine involved in cartilage degradation, was reported to connect with hyperalgesia and hypersensitivity in joint tissues [31]. This cytokine played a vital role in the progression of RA, as its level was found to increase in the serum and synovial fluid of arthritic patients [32]. Interleukin-6 reacted remarkably to primary afferent neurons [33], and hence it could play a role in pain transmission in arthritic states. In the skeleton system, IL-6 triggers osteoclasts and stimulates the synovium to produce MMPs that are responsible for degrading cartilage in OA [34]. Therefore, inhibiting IL-6 over-expression in synovial fibroblasts (SF) is believed to be an auspicious method to prevent OA progression, in which the clarification of molecular mechanisms underlying IL-6 over-expression in SF is essential.

4. Conclusions and Future Direction on Therapy for Osteoarthritis

A conservative controlling of osteoarthritis cannot discourse the major cause of the disease, when the application of agents is used alone. Additionally, these agents are not acceptable for long-term control of osteoarthritis, as they display major side effects. In contrast, varieties of natural products show protective effects against proinflammatory cytokine-induced expression and the catabolic activity of MMPs in articular cartilage, via the regulation of the NF-κB signaling pathway. Natural products exhibited inhibitive effects on the apoptosis in chondrocytes, and decline in the production of the ECM in articular cartilage. Nevertheless, although several preclinical and clinical studies are directed so far in natural product chemistry, still there are no perfect natural products recommended as an antagonist to the progression of the symptoms of osteoarthritis. This review might provide absolute readings about how natural compounds are beneficial for the treatments of joint diseases. Additionally, the information of the chondroprotective mechanism of natural substances would afford new opportunities to promote therapeutic strategies projected at encouraging destructive joint disorders.

References

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