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The Role of Proteinases in Osteoarthritis: A Brief Review of New Potent Cartilage Metabolism Therapeutic Target

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Abstract

Osteoarthritis (OA) is the most frequent form of degenerative joint disease that becomes a major source of disability worldwide. The loss of articular cartilage is the central etiology of osteoarthritis. Cartilage is solely composed of one cell type, the chondrocytes, which are surrounded by a large volume of extracellular matrix (ECM). Extracellular matrix components consist of two main macromolecules, namely collagen and aggrecan. The degradation of these molecules plays a significant role in OA pathological process, although degradation of less abundant molecules composing the matrix organization is also likely to contribute to disease progression. Several proteinases, including matrix metalloproteinase 13 (MMP-13) and A Disintegrin And Metalloproteinase with Thrombospondin Motifs (ADAMTS) -4 and -5, are known to involve in the matrix degradation of cartilage structure. A comprehensive understanding of the various factors and pathways involved in the regulation of MMP-13, ADAMTS-4, and ADAMTS-5 is essential in regard to osteoarthritis management, as they have great potential in future therapies.

Keywords: Osteoarthritis, Matrix metalloproteinase, ADAMTS, Cartilage, Connective tissue.

INTRODUCTION

Osteoarthritis (OA) is the most frequent chronic degenerative joint disease that becomes a major source of disability worldwide [1]. It mainly affects adults and the elderly population by causing pathological changes in the load-bearing joints that subsequently lead to degradation of articular cartilage, inflammation of the synovium (synovitis), the transformation of subchondral bone, and development of new bony growth at the joint margins (osteophytes) [2]. Several factors contribute to OA pathogenesis, such as aging, genetic predisposition, epigenetic factors, gender, obesity, exercise, trauma. These risk factors cause alteration in the physical, functional, and metabolic composition of the joint tissues, including synovium and bone, which are formed from various cell types and components of the extracellular matrix (ECM) [3].

The loss of articular cartilage precedes the primary pathological process of OA. Chondrocytes are the main cellular component of the cartilage, which is surrounded by a large volume ECM. The matrix can be divided into three zones based on their distance from the chondrocyte and matrix composition. The pericellular matrix is localized closely adjacent to the chondrocyte. It is enriched with perlecan, type VI collagen, and numerous regulatory molecules and growth factors that help to modulate the cell function. The next zone is the territorial matrix; then, the outermost zone is the interterritorial matrix with the main components of type II collagen and aggrecan. Collagen fibers have tensile properties that provide strength against stress-bearing loads. Aggrecan is the main cartilage proteoglycan that moves water into the matrix to swell and expand, allowing it to resist compression [4].

The molecular mechanism involving highly-expressed proteolytic enzymes, i.e., the matrix metalloproteinase 13 (MMP-13), A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) -4 and -5, are likely responsible for the degradation of structural components that maintain

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cartilage integrity; thus, contribute to osteoarthritis progression [4]. Currently, the treatment of OA is generally limited to symptomatic relief or surgical replacement of affected joints. This review highlights the pathological role of proteinases in the degradation of aggrecan and collagen. A comprehensive understanding of their molecular expression and activity is expected to form the basis for developing potential targeted therapies in the future management of OA.

PROTEASE ENZYMES IN EXTRACELLULAR MATRIX DEGRADATION

The degradation of articular cartilage characterizes the development of OA. The cartilage network is made up of two main extracellular matrix (ECM) macromolecules, namely type II collagen and aggrecan, which is a large aggregating proteoglycan [5]. The equilibrium between synthesis (anabolism) and degradation (catabolism) builds up a normal cartilage ECM metabolism. Pathological destruction of cartilage occurs when there is an imbalance between degradative proteinases, also known as proteolytic enzymes and their inhibitors. The matrix metalloproteinase (MMPs) and two aggrecanases, i.e., a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) -4 and -5, are two protease enzymes that play a significant role in the breakdown of cartilage in osteoarthritic joints [6].

Matrix Metalloproteinases (MMPs)

Chondrocytes are the solely cellular component of cartilage. Physiologically, they help maintain a balance between anabolic and catabolic activities required to preserve the structural and functional integrity of the cartilage tissue. The chondrocytes express numerous proteolytic enzymes, including the aggrecanases and matrix metalloproteinases (MMPs), responsible for maintaining cartilage remodeling under normal, very low turnover conditions [7]. However, under pathologic conditions, as in OA, excessive production of these enzymes occurs considerably, resulting in aberrant cartilage destruction.

The MMPs are a large family of structurally related calcium- and zinc-dependent proteolytic enzymes involved in the degradation of many different components of the ECM [8]. They are expressed in a number of different cell types and play a key role in diverse cellular processes ranging from morphogenesis to tumor invasion to tissue remodeling. Among all MMPs, MMP-13 (collagenase 3) is considered to be of particular interest due to its role in cartilage degradation. This enzyme plays a role in degrading type II collagen, which is the main type of collagen in the cartilage. Overexpression of MMP-13 in the pathogenesis of OA has been previously studied [9]. Given their important role in cellular functions, the biological expression and activity of MMPs are strictly regulated at multiple levels of gene transcription, synthesis, and extracellular activity. A complete understanding of the various factors and pathways involved in the regulation of MMP expression could be of interest concerning potential therapies [10].

Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS)

Lately, a second significant proteinase group that influences ECM synthesis and degradation has been identified. A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family consist of 19 members [11]. Some of them are involved in collagen biosynthesis as procollagen propeptidases (ADAMTS-2, ADAMTS-3, and ADAMTS-14) [12]. Meanwhile, other members of the family have a significant role as aggrecanases (ADAMTS-1, ADAMTS-4, ADAMTS-5, ADAMTS-9, and ADAMTS-15), which can be activated to degrade the interglobular domain that separate G1 and G2 of aggrecan at a specific Glu^{373}–Ala^{374} bond (Fig. 1) [13]. The cleavage within this interglobular domain can be also be mediated by MMPs, specifically at the Asn^{341}–Phe^{342} bond. Both activities can be identified in the articular cartilage of the arthritic joint [14].

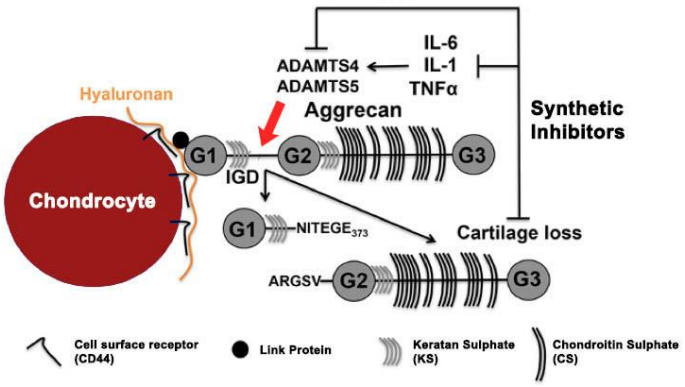

Figure 1: The mechanism of aggrecanase-mediated aggrecan degradation within the extracellular matrix around the chondrocyte. The interleukin (IL) and tumor necrotizing factors-alpha (TNF-α) induces the expression of the proteolytic enzymes ADAMTS-4 and ADAMTS-5. They furtherly target the interglobular domain (red arrow), which leads to the aggrecan cleavage in its C-terminal chondroitin sulfate (CS)-rich domains, specifically at the ARGSV (Glu^{373}–Ala^{374} bond). This contributes to pathological cartilage loss in osteoarthritis. Inhibitors of ADAMTS help prevent cartilage loss directly [16].

An *in-vitro* study done by He *et al*. established the activation of ADAMTS-4 and MMP-13 in the late stage of TNF-α oncostatin M (OSM)-stimulated bovine cartilage. In contrast, no significant activation of ADAMTS-5 was detected. This study emphasized that ADAMTS-4 is the major protease expressed in arthritic-induced bovine cartilage [15]. Existing data support the hypothesis that aggrecanases are actively involved in the disease progression, which is also co-assisted by the involvement of the MMPs. Thus, ADAMTS can be included as one of the enzymes responsible for cartilage aggrecan degradation at any stage of arthritis.

MECHANISM OF INHIBITION BY THE TISSUE INHIBITORS OF METALLOPROTEINASES (TIMPs)

Tissue inhibitors of metalloproteinases (TIMPs) are the endogenous inhibitors of the MMPs and several members of the ADAMTS families [17]. The mammalians mainly express four types of TIMPs (TIMP-1, -2, -3, and -4), which are known to have strong inhibitory activities against various types of MMPs, exceptionally MT-MMPs, which are poorly inhibited by TIMP-1. The TIMP-1 is able to inhibit ADAM10, while TIMP-3 is able to inhibit ADAM10, -12, -17, -28 and -33 as well as ADAMTS-1, -2, -4, and -5 [18].

The TIMP-3 acts to inhibit both collagenases and aggrecanases; thus, it becomes the central inhibitor for regulating the cartilage ECM degradation pathway. The mechanism action of exogenous TIMP-3 has been demonstrated to inhibit cartilage breakdown in a surgical osteoarthritic rat model [19]. The chondroprotective role of TIMP-3 is also confirmed by the finding of increased cartilage degradation upon aging in the TIMP-3-null arthritic mice model [20].

Other studies regarding the susceptibility of TIMPs-null mice in the development of OA have not yet been reported. Nonetheless, the inhibitory activity of TIMP in deteriorating the cartilage metabolism leading to OA progression can be discovered in other animal models study. The TIMP-2 showed a slight effect on aggrecan degradation in bovine, porcine, and human cartilage. The TIMP-1 revealed aggrecan degradation inhibitory activity in humans, but not bovine or porcine cartilage. Another study found insignificant alteration of the TIMP-3 mRNA levels in OA, while TIMP-4 expression was reduced in OA cartilage [21].

MMP-13 INHIBITORS AS POTENT OSTEOARTHRITIS TREATMENT

The inhibition of MMP-13 has been found to completely blocked the type II collagen degradation in both explanted animals and human

cartilages, proving its role as the primary collagenase in the OA. Therefore, the development of synthetic MMP-13 inhibitors drugs may become potential agents in the future management of OA [22]. In an animal model study, the utilization of selective MMP-13 inhibitors reduced cartilage destruction by 75%. Hence, a dose-dependent reduction in clinical symptoms and cartilage erosion was observed by 38% (30 mg/kg), 28% (10 mg/kg), and 21% (3 mg/kg) [23].

Natural ingredients have been the source of several MMP-13 inhibiting molecular activity. Jia *et al*. demonstrated the use of a 10 ng/ml dose of garcinol, originally made from the fruit rind of *Garcinia indica*, has been proven as an inhibitory agent in the expression of MMPs. It also promoted the synthesis of the main components of ECM and reduced the inflammation process that leads to the development of arthritis [24]. However, natural compounds are generally do not act selectively on MMP-13 due to potential binding to other substrates.

Several selective MMP-13 inhibitory agents have been synthesized and classified into biologically selective and chemically selective agents [25]. Monoclonal antibody (mAb) therapy is a biological agent that acts by immunologically targeting OA inhibition. In-vitro development of anti-MMP-13 mAbs was undertaken to selectively bind the MMP-13 and interfering with its functionality in the cartilage degradation pathway [26]. The N-O-Isopropyl sulfonamide-based hydroxamates series are identified as the zinc-binding MMP-13 inhibitor that acts through the attachment on the S1' subsite region of MMP-13 [27]. The compound 24f, generated from the carboxylic acid series, showed a potential inhibitory effect on the animal MMP-13 induced cartilage degradation [28]. The non-zinc-binding MMP-13 inhibitor, including diphenyl ethers, biaryls (aryltetrazoliums, arylfurans, pyrazole-indoles), pyrimidines, and aryl/cycloalkyl-fused pyrimidines, were also discovered to bind to MMP-13 specifically and inhibit its action to slow down the cartilage degradation [29]. However, despite their impressive profile as the potential therapeutic agents in OA progression, the utilization of these agents cannot be completely realized because they require high costs and require further evidence-based research to ascertain the benefits or harmful effects on osteoarthritic individuals.

ADAMTS INHIBITORS AS POTENT OSTEOARTHRITIS TREATMENT

An experimental study by Endrinaldi *et al*. revealed the immunosuppressive effect of mesenchymal stem cell Wharton Jelly (50 µl MSC-WJ by 1 x 10^6 cells dosage) in decreasing ADAMTS-4 levels on the monosodium iodoacetate (MIA)-induced OA rats [30]. On the other hand, certain hyaluronate (HA) species have also been proved to protect against cartilage degradation. Yatabe *et al*. found the inhibitory effect of high-molecular-weight HA (2700 kDa, HA 2700] on the expression of aggrecanases. It was found to downregulate IL-1α-induced ADAMTS-4 in human's isolated OA cartilage [31]. Seuffert *et al*. investigated the role of the upper zone of the growth plate and cartilage matrix-associated protein (Ucma) on its interaction with ADAMTS-5. They found a potential inhibition of destructive aggrecanolysis within the chondrocytes, both *in-vitro* and *in-vivo* cultures [32].

Several bioactive compounds have shown a potential effect on ADAMTS inhibition. The luteolin, an extracted nutraceutical flavonoid, is recognized as a novel and potential alternative in animal-models arthritic joints by inhibiting the ADAMTS-4 and -5 activities [33]. Scotece *et al.* established the potential effect of oleocanthal (OC) as a phenolic compound derived from extra virgin olive oil (EVOO) in inhibiting the progression of OA in humans. These compounds act on chondrocytes and are able to inhibit the effects of MMP-13 and ADAMTS-5 in inducing cartilage degradation. In addition, this compound also acts to inhibit several pro-inflammatory factors, including IL-6, IL-8, TNF-α, which are several molecules that play a role in the pathogenesis of OA (Fig. 2) [34]. Zheng *et al.* investigated another potential agent, the Silibinin, a polyphenolic flavonoid derived from fruits and seeds of *Silybum marianum*. This agent significantly decreased the expression of MMP-13 and ADAMTS-5 while increasing the expression of type II collagen and aggrecan in OA mice models [35].

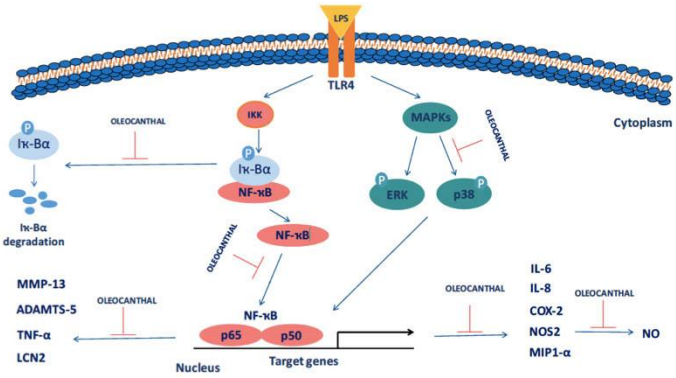

Figure 2: The inhibitory mechanism of the oleocanthal against the MMP-13 and ADAMTS-5 on the chondrocytes of human osteoarthritic subjects [34].

CONCLUSION

Many studies have discovered various agents with their unique potential inhibitory effects on the proteinases triggering osteoarthritis, including the MMP-13, ADAMTS-4, and ADAMTS-5. The relationship between these proteinases showed their significant role in OA progression; thus, the utilization of the agents to inhibit their activities shows excellent potential as the therapeutic target in the future management of OA. Nevertheless, further research is still needed to evaluate their bioavailability and efficacy in humans.

Competing interests

Authors have declared that no competing interests exist.

Authors' Contributions

The authors contributed equally to the literature search and interpretation of the relevant findings, study conceptualization, writing of the article, and manuscript revision. All authors have read and approved the final manuscript.

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