Original Research Article

Novel Biomolecular Target for OA Therapy

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ABSTRACT

Osteoarthritis (OA) is a chronic degenerative joint disease that affects many people worldwide, in which the loss of articular cartilage is the main cause of the pathology. The anatomical changes of OA include cartilage degradation, inflammation of the synovium, subchondral bone changes, and osteophyte formation. Damage to or loss of the extracellular matrix (ECM) composed of collagen, proteoglycan, and water, serves as the pathologic process of OA. The current available treatment options only include symptomatic or pain relief and surgical procedures toward joint replacement for correcting the deformity as a severe complication of OA. These, however, do not provide an adequate strategy for slowing the progression of OA, not to mention completely ceasing or reversing the resultant joint damage. Consequently, several alternatives for OA management have been recently proposed, including therapies targeting several enzymes and substrates playing important roles in OA, namely proteases, aggracanases, matrix metalloproteinases, and sialic acid.

Keywords: Osteoarthritis, protease, aggrecanase, sialic acid
https://doi.org/10.31282/joti.v4n3.79

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INTRODUCTION: OSTEOARTHRITIS

Osteoarthritis (OA) is a chronic degenerative joint disease affecting many people globally. It may cause disability, joint stiffness, and even the loss of joint function, especially in the older population. Anatomical changes occurring in OA include cartilage degradation, synovial inflammation, subchondral bone changes, and finally osteophyte formation.[1]

Nowadays, the management of OA is only symptomatic and surgical, namely joint replacement.[2] There is no single medication that can completely cure or prevent OA from becoming a full-blown disease. Therefore, a novel therapeutic strategy has been developed to target the main cause of OA, which is the loss of cartilage. To date, a biomolecular approach in the treatment of OA can be a promising novelty in order to improve patient's quality of life.

PATHOPHYSIOLOGY OF OSTEOARTHRITIS

The underlying etiology of OA is not fully understood; however, several mechanical factors have been associated with its development and progression. These factors include injury and obesity, along with other risk factors like age, gender, or genetics. The main pathology of osteoarthritis is a degenerative process involving the cartilage breakdown and, finally, the dysfunction of joints.

Cartilage is tissue formed by chondrocytes and surrounded by an extracellular matrix (ECM). Water, collagen (especially type II collagen), and proteoglycan build up this ECM. Collagen contributes to the strength of the cartilage to sustain tensile, while the proteoglycan absorbs water to sustain compression. Damage to or loss of these two important components, collagen and proteoglycan, are the main pathologies in OA.[3] Several enzymes are also responsible for ECM degradation, including matrix metalloproteinase (MMP), aggrecanases, serine proteinase, and cysteine proteinase.[4,5]

Type II collagen is the most common collagen found in cartilage. This type II collagen forms a fibril-woven structure. As previously mentioned, collagen degradation and the activity of aggrecanases are the main features of OA. Aggrecan plays an important role in protecting collagen from degradation. Although damage to proteoglycan is reversible by nature, damage to collagen is irreversible and cartilage repair would be impossible if the collagen were damaged.[6,7]

Matrix metalloproteinases (MMP) are endopeptidases bound to zinc that contribute to growth, development, wound recovery, and various pathological conditions, including arthritis and cancer. Its main role is to degrade ECM.[8] It has been observed that several MMPs are secreted by osteoblastic cells, including MMP-2, MMP-3, MMP-8, MMP-9, MMP-13, and MT1-MMP, while MMP-9 is mainly expressed by osteoclasts. MMP has been proven to degrade osteoid and activate bone remodeling in experimental animals and humans. MMP-13 is considered essential for osteoclastogenesis and is primarily associated with the mineralization of bone matrix. It also plays an important role in the degradation of type I collagen in the bone matrix. Abnormal expression of several MMPs in osteoblastic cells is also observed in patients with estrogen deficiency, since estrogen decreases MMP-13 levels in osteoblastic cells, resulting in inhibition of bone resorption and a decline in the rate of bone turnover.[9-11] MMP-13 is mainly produced in human chondrocytes in normal circumstances, but it undergoes rapid endocytosis and degradation. It is mainly expressed in OA cartilage but not in normal cartilage. According to several previous studies, MMP-13 levels in synovial fluid are known to correlate with the severity of OA. High expression of MMP-13, which induces joint abnormalities in OA, was observed in studies using a transgenic animal model. Studies evaluating MMP-13 inhibitors observed that MMP-13 inhibition provided protection against human and bovine cartilage cultures and provided an in vivo chondro-protective effect.[12,13]

OA, being one of the most common forms of arthritis, is characterized by joint cartilage destruction. Collagen type II, along with various proteoglycans, including aggrecans, chondroitin sulfate, and hyaluronan, are the main constituents of the joint tissue. The triple-helical structure of collagen type II contributes to the tensile strength of joint cartilage. Meanwhile, MMP-13 has been observed to be a major collagenase responsible for joint cartilage degradation in OA. The initial alteration of OA in animal and human models is controlled by a significant up-regulation of MMP gene expression. This MMP gene expression is increased by proinflammatory cytokines produced by activated synoviocytes or chondrocytes, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α.[12,14]

Another important process contributing to the pathogenesis of cartilage destruction is mechanical

stress. In numerous in vivo and in vitro experiments, MMP-13 seemed to be involved in the early stages of OA development. In a mouse model of mechanical stress-induced OA, Kamekura et al. found MMP-13 in the early stages of OA in vivo. MMP-13 expression rose rapidly in chondrocytes in vitro due to mechanical stress.[15] There are more than 20 proteinase enzymes that make up MMP, each of which is a product of a variety of different genes. Some MMPs are created in abundance by chondrocytes and synovial cells in inflamed or arthritic joints. There are five sub-groups of MMPs according to their substrate specificity: collagenase, stromelysin, gelatinase, and membrane-type MMP.[16]

Four membrane-type MMPs (membrane-type MMP/MT-MMP) have been identified in cartilage tissue, namely MT1-MMP (MMP-14), MT2-MMP (MMP-15), MT3-MMP (MMP-16), and MT4-MMP (MMP-17). It has been shown that chondrocytes and synovial cells express "membrane-related members" of the MMP group (except MMP-14) at low levels. MT1-MMP is the most dominant in cartilage tissue and is regulated by various cytokines (TGF-beta1, IL-1beta, and TNF-alpha) and epidermal growth factors (EGF). Additionally, the MT1-MMP is also capable of initiating the activation of pro-MMP-2 and pro-MMP-13. These two enzymes are specifically believed to be involved in mediating type II collagen webbing structure breakdown in cartilage tissue.[17,18]

Various other proteinases are further classified as disintegrins and metalloproteases with the recurrent thrombospondin family (ADAM-TSx), in which they can digest the core aggrecan protein. They have been identified and named aggrecanase-1 and aggrecanase-2, respectively. Various cytokines (IL1-beta, IL-6, IL-17, and TNF-alpha) and EGF regulate these aggrecans with a mechanism that differs from MMP regulation. Aggrecanase-2 creates a different "abrasion site" than that produced by MMP (Asu341-Phe342) in aggrecan molecules. In addition, it was recently discovered that aggrecanase-1 can cleave aggrecan molecules at the site of action of MMP (Glu373-Ala374).[8]

Tissue inhibitors of metalloproteinase (TIMP)-1, TIMP-2, TIMP-3, and TIMP-4 can inhibit MMP. According to previous studies, once TIMP is activated, it can inhibit MMP, and the balance between MMP and TIMP is indispensable in maintaining joint cartilage homeostasis. TIMP-3 has also been shown to inhibit aggrecanase activity in vitro.[19]

The synthesis rate of MMP in cartilage with OA far exceeds the up-regulation of TIMP-1, -2, -3, and -4 gene expression. Even though the expression of TIMP-1 mRNA by chondrocytes in cartilage with OA is higher than that in normal cartilage, the chondrocytes in OA do not produce sufficient amounts of the TIMP isoform to inhibit the existing MMP levels. MMP will degrade both endogenous and the newly synthesized ECM molecules. Finally, this process will result in the total loss of cartilage integration.[12]

DAggrecan is one of the main constituents of articular cartilage ECM and is largely responsible for the high resistance to compression of this load-bearing tissue. Its high osmotic pressure from the negatively charged GAG2 chains gives rise to the resistance to compression of the cartilage. The formation of aggregates is physiologically critical for the retention of aggrecan in collagen tissue.In numerous pathological conditions, including OA, the degradation of ECM macromolecules outperforms their synthesis, resulting in a decreased net cartilage matrix.[20]

Cartilage aggrecan degradation was initially assumed to only involve MMPs. But over time, other enzymatic activities have been proposed to be responsible for the response to the breakdown of aggrecan core molecules and proteins in the peptide bonds Glu373-Ala374 in the interglobular domain of these molecules. Aggrecanase is the term to describe this enzymatic activity. Many researchers throughout the 1990s debated whether aggrecanase belonged to the MMP group. The debate ended in 1999 when the ADAMTS group, a disintegrin and metalloproteinase with thrombospondin, was first introduced. This protease was initially named aggrecanase-1, also known as ADAMTS4, and sometime later, aggrecanase-2, or ADAMTS5, which has a specificity like that previously identified.[20-22]

It is also suggested that ADAMTS5 is present in human chondrocytes and synovial cells. The increased expression of ADAMTS5 mRNA in chondrocytes and synovial cells is not influenced by stimulation of IL-1, TNFα, or TGFβ, unlike ADAMTS4, whose levels are influenced by other cytokines. However, several follow-up studies showed different regulation of ADAMTS5 mRNA expression in bovine chondrocytes, in which the enzyme responded to IL-1 stimulation, unlike ADAMTS4 mRNA expression.[20,22]

TIMP-3 is a potent biological inhibitor to inhibit ADAMTS5 activity with *K*i values only in the subnanomolar range. The interaction between aggrecan and the C-terminal domain of ADAMTS5 can modulate it well. TIMP 3 is the only TIMP that hinders ADAMTS5 activity, although there are still many other TIMPs.[22]

Aggrecan constitutes the main proteoglycan in cartilage, and therefore severe damage, which has been associated with its aggrecanase action, is an important manifestation of OA. Aggrecanase was identified as the proteinase responsible for cleaving the matrix proteoglycan and can increase in its level in several circumstances; this activity is a feature of cartilage degradation during inflammatory diseases such as OA. A rise in the cleavage of ADAMTS family proteins at the aggrecanase site has been shown in vitro. Of these, ADAMTS-4 and ADAMTS-5 are the most efficient aggressors and have generally been proposed as the most likely candidates for a role in the pathological mechanism of OA. Significant protection against ex vivo proteoglycan degradation and decreased OA severity is provided by ADAMTS-4 and ADAMTS-5 in animal models. ADAMTS-4 and ADAMTS-5 both play important roles in mediating aggrecan loss in normal cytokine-stimulated cartilage and the ongoing degradation seen in cartilage OA. Consequently, a potential therapeutic strategy for OA can be directed towards the inhibition of their proteinase activity.[11,20]

In cultured bovine and swine chondrocyte models or cartilage explants, ADAMTS4 was induced after stimulation with IL-1, TNF-α, oncostatin M or transforming growth factor (TGF), but not ADAMTS5. A recent study showed that although ADAMTS4 gene expression could be increased through treatment with IL-1, TNF- α or oncostatin M, there was little effect on ADAMTS5 in either human chondrocytes or cultured human cartilage explants. On the contrary, an additive effect of combination treatment with oncostatin M and either IL-1 or TNF- α in this system was present, and this led to induction of ADAMTS4 as well as some induction of ADAMTS5 gene expression. In the synovium or cartilage undergoing OA, the aggressiveness of the activity and the expression of ADAMTS4 and ADAMTS5 are present constitutively, without the requirement for catabolic stimulation. Previous studies showed that ADAMTS4 upregulation relies on TNF- α and IL-1 produced by synovial macrophages, whereas these cytokines do not alter ADAMTS5 levels.[22]

In bovine nucleus pulposus tissue, upregulation of aggrecanase activity, ADAMTS4 in particular, in an NFkB-dependent manner, is induced by TNF treatment, although the specificity of the small NFkB inhibitor molecule used in this study remains unproven. In human OA synovial fibroblasts, upregulation of ADAMTS4 was observed in treatment with IL-1 or TNF-a but not with phorbol ester, while ADAMTS5 was unaffected. In this model, NFkB can be specifically inhibited by adenoviral gene transfer from the endogenous inhibitor IkBa without affecting other signaling pathways or causing apoptosis. Whereas ADAMTS5 gene expression was not altered by IkBa gene transfer, NFkB regulation potentially inhibited ADAMTS4 induction by IL-1 or TNF-a. A loss of the IL-1 response to the luciferase gene reporter vector ADAMTS4 results from mutation of one of the three identified NFkB binding sites, indicating that two or more NFkB binding sites located in the region 5 'flanking of this gene highly affect the increased transcription of the IL-1 stimulated ADAMTS4 gene.[23] These studies strongly suggested that the upregulation of ADAMTS4 induced by IL-1 or TNF-a is NFkB dependent. However, the role of NFkB in regulating ADAMTS5 expression remains unproven.[24,25]

Sialic acid, a form of carboxylated sugar, has a distinct pattern and tissue specificity. It can occur in free form or as constituents of glycoproteins and many forms of saccharydes, including polysaccharides, oligosaccharides, lipopolysaccharides, and lipooligosaccharides. Besides, membrane anchors and keratan surfaces have also been shown to contain sialic acid.[26] Cell behavior, including its growth, migration, inflammation, and matrix production, highly depends on specific sialylation motifs that lead to different effects of glycoproteins. Glycosilation is an important process in modifying cell surfaces and ECM proteins. In articular cartilage, chondrocytes and ECM high in collagen and proteoglycan have a high content of glycosylated proteins, and there is a thick coating of carbohydrates on the cell surfaces. The glycosylation process is heavily involved in the modification of the cell surface and ECM.Arthritis has been shown to be associated with a change in glycoproteins containing certain chains of sialic acid. Recent studies showed that OA cartilage expresses sialylated transmembrane mucin receptors.[27,28]

The interaction between glycan-binding proteins (GBPs) and glycan-protein interactions are essential for physiological or pathological process regulation, including inflammation and arthritis. Two major groups

of GBPs consist of lectins and glycosaminoglycan-binding proteins. Lectins function as identifiers for specific patterns of glycan molecules. Under pathological circumstances, the interaction between lectin and glycan controls the activation of inflammatory pathways. For instance, galectin-1, a part of beta-galactoside-binding lectin, has been observed to induce inflammatory responses in OA through enhancement of the secretion of effectors of the degeneration process, including NF-B. Certain modifications in lectin and glycan result in the development and progression of certain disorders. In degenerative joint diseases, the expression of the -2,3-sialylated glycoprotein PDPN receptor stimulates degenerative joint changes by specifically involving tissue development, repair, and inflammation processes.[27]

MATRIX METALLOPROTEINASE-13 AS POTENTIAL TARGET THERAPY

The early pathological phase of chondrocytes is highly affected by MMP-13 since it promotes the release of the Low-density lipoprotein Receptor–related Protein-1 (LRP1) protein in cartilage. LRP1 plays an important role in regulating the clearance of ADAMTS-5. Therefore, to promote LRP1, MMP-13 interacts with another protein through activation of the latent form of the MMP-13 protein. A potential therapeutic target for early OA is the pro-MMP-13 activator because the activation of the zymogenic form of MMP-13 occurs rather early in the progression of OA. There are many other transcription factors involved during various stages of OA, these include LEF1, NF-κB, ELF3, HIF2α, and Runx2, in which they either directly or indirectly impact MMP-13 transcription.[9]

The chondrocytes and synovial cells produce MMP as a latent pro-enzyme. Thus, the process of OA involves several activation pathways, in which therapeutic intervention can be addressed on to these activation events. Plasminogen activator synthesized by chondrocytes synthesize plasminogen activator (plasminogen activator/PA) produce plasmin. It is known that the PA form found in urine (uPA) and tissue (tPA) are both produced by chondrocytes. The uPA form may be more important in the process of cartilage damage since plasmin, identified as a generalized MMP activator, is able to convert pro-MMP-13 into the active form of MMP-13. Pro-collagenase is then activated by this active form of MMP-13. The plasmin/PA pathway is regulated by a plasminogen activator inhibitor (PAI). The plasmin concentration is significantly higher than normal and the observed level of activated MMP is also higher in joint cartilage with OA. Another activation pathway has also been found in membrane-type MMP (MT1-MMP; MMP-14), activating MMP-2 (gelatinase A) and collagenase-3. Samples taken from patients with early-stage OA have also shown significantly increased MMP activity. Hence, therapeutic interventions can be directed and designed to inhibit MMP activity, and they will specifically be useful for managing OA.[11,19]

AGGRECANASE: ANOTHER POTENTIAL TARGET THERAPY

According to the most recent data presented in this review, while ADAMTS4 and ADAMTS5 were similar, they were two very different enzymes for their regulation. At least in human cells, ADAMTS4 responds to IL-1 and TNF-a, while ADAMTS5 does not. Another difference is that ADAMTS4 upregulation depends on the transcription factor NFkB, whereas ADAMTS5 is NFkB independent and has no kB element in its promoter. With this in mind, it is interesting to note that treatment to prevent IL-1-induced aggrecan depletion can be achieved through the use of the small molecule IkB kinase inhibitor in bovine cartilage explants, suggesting this process occurs in an NFkB-dependent manner. This dissimilarity in the regulation of ADAMTS4 and ADAMTS5 has implications for the potential development of disease-modifying osteo-arthritis medications. A therapeutic strategy inhibiting cytokine-induced inflammatory responses would tend to downregulate ADAMTS4, as would NFkB inhibitors. However, no strategy is likely to affect ADAMTS.[29]

The pharmaceutical industry has set its sights on the design of small-molecule aggrecanase inhibitors. For such an approach to work, there is a need to appreciate that ADAMTS4 and ADAMTS5 are configured differently. Further identification of the primary aggrecanases (ADAMTS4 or ADAMTS5) involved in human OA is therefore necessary.[24,30]

TARGETING SIALIC ACID IN OA PATHOGENESIS

Lectin, a type of sialic acid, has been utilized in differentiating malignant from benign tumors, and its use as a therapy for cancer by inhibiting cell proliferation has been widely proposed. Targeting sialic acid as therapy

for OA involves the regulation of signaling cascade events aiming to protect cartilage from catabolic effects inducing ECM degradation. Lectin has potential effects on cartilage structure and primary chondrocytes in which it preserves cartilage structure and function by interfering with the transmembrane receptors under multiple factors inducing arthritis. Regulation of signaling cascades would prevent catabolic effects inducing ECM degradation on the cartilage, so invasive therapeutic methods, namely surgery can be prevented. Sialic acid occurs in free form or as a constituent of glycoproteins and saccharides, important components of a cell, playing a role in its growth, migration, and inflammation. ECM and chondrocytes contain high levels of glycosylated proteins, and glycosylation is important in cell surface modification and ECM production. Since arthritis involves a change in glycoproteins with sialic acid resulting in degenerative joint changes, a specific therapy targeting sialic acid focuses on controlling the interaction and modification between glycan and lectin, a form of sialic acid, resulting in the inhibition of inflammation and degenerative changes.[26,27]

SUMMARY

OA is a complex degenerative joint disease in which the underlying pathologic process requires further understanding so that therapy can be aimed at preventing OA from happening, slowing the pathologic process, and preventing its complications rather than correcting the debilitating resultant deformity. Treatment strategies targeting proteinase, aggrecanase, and sialic acid offer a promising future to prevent further degradation in OA; however, further research on this topic is highly necessary as a whole new alternative to symptomatic therapy and joint replacement surgery commonly performed in OA.

Conflict of Interest

The author declares that there is no conflict of interest related to the material discussed in this manuscript.

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