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Specific Proteases for Osteoarthritis Diagnosis and Therapy

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1.1. Introduction

1.1. Osteoarthritis (OA)

1.1.1. Causes and Symptoms of Osteoarthritis

Osteoarthritis is the most common style of arthritis, and this complicated and chronic degenerative joint disease is extremely found in adults and especially in old people. It mostly affects the whole joint structures associated with progressive changes in cartilage, menisci, ligaments and subchondral bone.[1-3] The cartilage covers the end of joint bones and provides slippery touch during movement, so it is obvious that the degradation of the cartilage extracellular matrix is a central feature of this disease. Normal articular cartilage makes bones frictionless with each other, and additionally it can also reduce the damage caused by shock of movement.[4] However, in osteoarthritis the top layer of articular cartilage wears out and even breaks down, which initiates the bone rubbing against each other, and therefore causes pain, sclerosis, swelling and loss of organ function in joint. As time going on, the symptoms are increasing in frequency and severity, finally the shape of joint changes with deformity, bone spurs may also occur at the edges of joints, bits of bones even fractures and floats among the joint space.

According to the pre-existing investigations, osteoarthritis has affected the health of a growing number of people world-wide.[5] Though osteoarthritis will not endanger the life safety of sufferers, its occurrence and development may not only seriously threaten people’s physical fitness, but also directly reduce their quality of life.

It is well known that the loss of cartilage is concerned with the etiology of osteoarthritis.[1] The articular cartilage failure is triggered by several correlate factors, such as genetic, metabolic, and biomechanical factors with secondary components inflammation which react...
mutually. Until now the pathogenesis has not been wholly revealed due to the multifactorial pathological mechanism of osteoarthritis, though many groups have researched for a long time.[6-10] Moreover, other risk factors including obesity, older age, joint injury, family history, over using, bone density, defect in joint cartilage contribute to osteoarthritis progression.[11-14]

Based on the above description, it is not hard to see that there must be osteoarthritis syndrome with a series of heterogeneous presentations,[15] such as a) joint pain, also the major clinical manifestation; b) joint stiffness, especially morning stiffness; c) functional disorder, like joint instability and activity limitation. These symptoms of osteoarthritis develop slowly and get serious increasingly with time.

Osteoarthritis is short of the physical and biochemical integrity of a joint, and also presents as a mono-arthritis, oligo-arthritis or a poly-arthritis, with several distinct patterns which exist in most ethnic and racial groups.[16] The common feature of osteoarthritis is characterized by the early inflammation followed by degeneration of chondrocytes including irreversible biodegradation. Then osteoarthritis appears as transformation of whole joint structures including degradation of the articular cartilage, menisci and ligaments, and these are also accompanied by other performance, such as joint space narrowing (JSN), bone marrow lesions, synovial inflammation, changes of subchondral bone and generation of osteophytes at the joint edge (See Figure 1).[2, 10, 13, 17] The degradative process of cartilage is widely considered to be regulated by the protease involved in osteoarthritis.[4, 6, 10, 18]

![Diagrammatic presentation of normal and osteoarthritic joint.][10]

As the major mediators of collagen and proteoglycan cleavage, two classes of proteases are thought to be responsible for the degradation of cartilage components in osteoarthritis. It was thought that the collagen degradation is majorly due to the action of matrix metalloproteinase (MMP) collagenases. Mort et al. have indicated that members of both MMP and ADAMTS (a
disintegrin and metalloproteinase with thrombospondin motifs) families are important mediators of the degradation of proteoglycans.[19] At the same time there is evidence for the role of the cysteine protease cathepsin K in collagen degradation in articular cartilage as revealed by Konttinen et al.[20] The cleavage of cartilage proteins often occurs at specific sites on these molecules, resulting in the generation of characteristic N- and C-terminal epitopes which can be used for the production of antibodies specific for these cleavage products (anti-neoepitope antibodies).[21] Recent years, Chan et al. have also reported that the increased chondrocyte sclerostin may protect against cartilage degradation in osteoarthritis.[22]

1.2. Importance of osteoarthritis diagnosis and therapy

Currently the total number of osteoarthritis patients in world-wide is more than 600 million. There are about 1/6 of people in Asia suffering from osteoarthritis at some stage of their life, among which patients account for 10% of the total population in China, and are increasing in recent years. It is even estimated that the number may reach to 150 million by 2015. In addition, it has been reported that a lifetime risk of OA-specific morbidity of about 45% for the knee and 25% for the hip.[23] The National Healthy and Nutrition Examination Survey of USA points out that the symptoms and signs of clinical osteoarthritis are only in 12% of 6913 people, aged among from 25 to 74 years, and X-ray results of osteoarthritis appeared in at least one site occupy 33%.[24] It will be worse that 53% of osteoarthritis patients may lead to disability, loss of joint function and the ability to work.

Unfortunately, the disease-modifying drugs for osteoarthritis are not available currently, the drugs have the role of analgesic effect and symptom improvement, but they do not involve the OA pathology and change the abnormal structure. Even though some styles of drugs can slow down and reverse the degradation of cartilage, they produce the desired result tardily, and the curative effect only can maintain for a short period. Osteoarthritis has become the largest disease causing disability and is known as “no-lethal cancer”, it is so harmful to human health, and the related research about it has been carried out.[25-27]

While there is no complete cure for OA until now, the early detection followed by efficient therapy may slow down its detrimental effects. Apparently, a diagnostic system that enables early and reliable diagnosis of this degenerative joint disease is necessary,[28] such as biochemical test and imageological diagnosis (X-ray or/and NMR examination). a) biochemical test: recent years, the special biochemical marker have been drawn attention, hydroxylysyl-pyridinoline, heoxylysylpyridinoline, C-reactive protein, Serum amyloid A and so on are all used to calculate the OA; b) imageological diagnosis: the diagnosis base on radiology manifestation of OA through X-ray or/and NMR examination. However, the imaging technique can not accurately, selectively evaluate quantitative property of articular cartilage. In addition, once it is diagnosed as osteoarthritis, the disease has proceeded into the mid- or late- period, and the opportune moment and prompt treatment to patients are all missed, so the new technology and strategy need to be further developed. Treatments are also limited to relieve the symptoms and surgically replace the affected joints. Therefore, to minimize the damage, understanding the early symptoms of bone disease will help to detect and treat the disease. The development of bone-related diagnostic and therapeutic programs will be essential,[29] and a wide range of work in the past years has proved that several proteases might related directly to osteoarthritis.
2. Diagnosis of osteoarthritis in targeting specific proteases

2.1. Cathepsin B (Cath B)

As a cysteine proteinase, cathepsin B is a lysosomal cysteine protease, which belongs to the papain surper-family and has been implicated in the pathology of a number of important human disease, including cancer and arthritis.[30] It has been shown to be up-regulated in patients with rheumatoid arthritis,[31] and components of the extracellular matrix are shown to be substrates for this protease.[32] Cathepsin B is active in aggrecan and cartilage,[33-34] cleaves the aggrecan G1-G2 domain fragment, and engenders two fragments from the cleavage at Gly-Val bond to the metalloproteinase cleavage site. For example, Fosang et al. have revealed that cathepsin B degraded the proteoglycan extensively producing several bands of faster migration and therefore it can be used as a biomarker of diagnosis of OA.[35]

Then Lai’s group took twelve male nude mice to investigate early diagnosis of osteoarthritis on a molecular basis, by using the developed cathepsin B sensitive near-infrared (NIR) fluorescent probe.[36] Firstly, they injected collagenase (1.0%, w/v) into the right knee joint to induce osteoarthritis and the left knee joint served as a comparison. Secondly, the cathepsin B sensitive near-infrared fluorescence probe was activated, which could radiate an intensive NIR fluorescence signal. Finally, the NIR fluorescence signals were caught by an optical imaging system which could receive an emission wavelength of 680–720 nm. Using this mechanism, they discovered that 3-fold difference in signal intensity between osteoarthritic and normal joints can be detected after 24h intravenous injection (see Figure 2). Therefore, it is believed that cathepsin B activatable NIR fluorescence probe can offer a potential new imaging technology for early osteoarthritis diagnosis.

Figure 2. Near infrared fluorescence reflectance imaging, which were taken 24 h after intravenous injection of the cathepsin B sensitive auto-quenched probe in a representative animal; (A and B) white light images, (C and D) NIRF images.[36]
2.2. Lactate Dehydrogenase (LDH)

LDH-4 and LDH-5 play an important role in anaerobic metabolism of articular cartilage. In early 1975, Weseloh and Fiegelmann began to realize the importance of LDH-isoenzym patterns in human cartilage, and attempted to evaluate it. The result of experience was that LDH-5 dominates with an average of 75.3%, whereas the LDH-4 (21.7%) and the LDH-3 (3.2%) were considerably lower, which was significant for the later study. [37]

As we know from previous literatures, degenerative joint diseases were deemed to associate with increased LDH activity in the synovial fluid. In order to verify the distribution of LDH, Eveline et al. have made a study to examine healthy and degenerative stifle joints for the goal of clarifying the origin of LDA in synovial fluid through many technical means, such as transmission electron microscopy (TEM), immunolabeling and enzyme cytochemistry. And then all techniques corroborated that the presence of LDH in chondrocytes and in the interterritorial matrix of degenerative stifle joints. Whereas LDH is retained in healthy cartilage due to permeability limitations, it is released into synovial fluid through abrasion as well as through unrestricted diffusion as a result of degradation of collagen and increased water content in degenerative joints.[38]

In addition, the spectrophotometric technique using the pyruvate to lactate conversion was taken to measure the total LDH activity, while agar gel electrophoresis followed by a tetrazolium enzymatic staining reaction was used to establish the LDH isoenzyme patterns. Veys et al. have found long before that the cases of arthritis had high LDH activity both in cellular material and in cell-free fluid. Moreover, these cases also had an increased percentage of LDH-5 in the cellular extract. It was concluded that the LDH could be a symbol reflecting the degree of arthritis and used to the diagnosis of early OA.[39]

3. Therapeutics of osteoarthritis in targeting specific proteases

3.1. Sclerostin (SOST)

Sclerostin is a kind of extracellular protease (see Figure 3). As it is well known, the SOST gene encodes for the secreted protein sclerostin.[40] The expression of SOST in the adult body exclusively is produced by osteocytes located in bones. Therefore, sclerostin is considered as negatively modulating osteoblast development and bone formation.[41-42]

At first it was thought that sclerostin might implement its regulatory function via acting as a modulator of bone morphogenetic proteins (BMPs).[43] Afterwards the accumulating evidence showed that sclerostin interferes with the Wnt signaling pathway due to binding to the Wnt co-receptor LRP5 and consequently regulating bone growth.[44-45] SOST restrained the express of Wnt signaling, which was important in the skeletal development[41, 46] and could regulate the activity of β-catenin. It was also reported that excess SOST could lead to chondrocyte apoptosis and cartilage damage, namely arthritis, through suppressing the normal function of β-catenin.[47] At the same time, the study performed by Blom et al. have shown that superabundant β-catenin would produce a procatabolic effect in the cartilage and promote
chondrocyte hypertrophy directly related with osteoarthritic pathology. Therefore, moderate sclerostin would be necessary to keep β-catenin at an appropriate level, and it would be a crucial indicator in the treatment or diagnosis of osteoarthritis.[48-50] Of note is that, the importance of Wnt/β-catenin signaling in the pathogenesis of osteoarthritis in humans has not been well understood. For example, the findings in preclinical studies using anti-sclerostin therapy in animal models of osteoarthritis have been disappointing, with no reported benefit on cartilage remodeling during aging or mechanical injury.[50] In addition, the role of sclerostin in the pathogenesis of osteoarthritis in humans has not yet been well defined, and the potential utility of treating osteoarthritis with interventions that alter sclerostin is not known. Still, we are surely pleased to see that summary of SOST in therapeutics of OA will be performed.

3.2. Matrix Metalloproteinases (MMPs) and Adamalysin with Thrombospondin Motifs (ADAMTS)

A significant characteristic of osteoarthritis is the degradation of the extracellular cartilage tissue. According to the previous reports it is widely known that the structural component of the matrix is mainly composed of collagen and aggrecan, which are regulated by the proteolytic enzymes, MMPs and ADAMTs.

3.2.1. MMPs

The collagen found primarily in the cartilage ECM is type II collagen, which appears as the fibrillar network (see Figure 4) and offers strong elasticity to the cartilage matrix. It will be difficult to be repaired for cartilage once the collagen was lost (see Figure 5).[52-53] Matrix
metalloproteinases (MMP) comprises a family of zinc-dependent enzymes, they are called collagenases which possess the collagenolytic abilities that degrade extracellular matrix components.[54] These proteases regulate the initial cleavage of the collagen triple helix, occurring at 3/4 of the distance from the amino-terminal end of each chain, forming collagen fragments of 3/4 and 1/4 length.[55] To be directly related to these processes there are three kinds of collagenases: collagenase-1 or interstitial collagenase (MMP-1); collagenase-2 or neutrophil collagenase (MMP-8); and collagenase-3 (MMP-13). In addition, MMP-13 is considered as the primary collagenase in collagen degradation.[6-57] Neuhold et al. showed that MMP-13 transgenic animals exhibited joint pathology which strongly resembled osteoarthris. Such a result provided direct evidence in support of a role for this proteinase in the pathology of this disease.[18]

3.2.2. ADAMTS

Aggrecan is a large proteoglycan including chondroitin sulphate and keratan sulphate glycosaminoglycan moieties, and is crucial for bringing water to the cartilage matrix which gives joints the ability to bear the heavy load. Aggrecan plays such a good role, short of it can lead to the articular cartilage softening and loss of fixed charges, then the joint function will be reduced and even forfeited.[58] Aggrecan molecules possess two major cleavage sites in the interglobular domain (IGD) region of the core protein. Without the G1 domain, aggrecan molecules can be free in and out of the cartilage matrix, leading to the lack of cartilage function.[59] The first cleavage site at the Asn341-Phe342 bond, creating the neoepitope VDIPEN, is found to be generated by MMPs.[60] The second site at the Glu373-Ala374 bond, creating the NITEGE neoepitope, is found to be very important and results from aggrecan cleavage, which is associated with lots of pathologies.

![Figure 4](image-url) Electron micrographs of healthy cartilage. a) A dense superficial network of collagen fibers running in parallel with the articular surface is present. Chondrocytes contain numerous organelles and vesicles. Inset An amorphous layer (double arrow) extends at the surface. Underneath, densely packed collagen fibers run in parallel with the articular surface. b) Territorial (A) and interterritorial (B) zones of extracellular matrix are clearly demarcated. Note the large nucleus and abundance of organelles in the chondrocyte.[38]

Related studies have shown that ADAMTS-5 is a pivotal enzyme for cutting the Glu373-Ala374 bond, and the inhibitors of ADAMTS-5 can debase the aggrecan decomposition effectively. So ADAMTS-5 is important in osteoarthritis of individuals and responsible for aggrecan degra-
A new drug, AGG523, in targeting ADAMTS-5 and ADAMTS-4 for therapeutics has entered clinical trials phase I. Studies by Glasson et al. and Majumdar et al. carried out with ADAMTS-5 knockout and ADAMTS-4/-5 double knockout mice showed that these animals were more resistant to cartilage degradation after destabilizing knee surgery.[62-63] However, in human, assumed damaging polymorphisms in the ADAMTS-5 gene does not show any modification in selectivity to osteoarthritis.[64] The search for the most important aggrecanase in human osteoarthritis is still going.[65]

3.3. Cathepsin K

Cathepsin K (Cath K) is a cysteine proteinase of papain family. It has been implicated in the resorption of the bone matrix. Like most of the proteinases, cathepsin K is synthesized and secreted from the cell as an inactive proenzyme, it should be noted that cathepsin K is secreted from macrophage and synovial fibroblasts. Cathepsin K cleaves the triple-helical type II collagen[66], and the special distribution of cathepsin K in osteoarthritic cartilage suggests an important role of this protease in the etiopathogenesis of osteoarthritis.

Early in 2004, Morko et al. took transgenic mice which were predisposed to early osteoarthritis because of harboring a short deletion mutation and their non-transgenic litter mates as controls for study.[53] They used the immunohistochemistry and morphometry to investigate the distribution of cathepsin K in the knee joints. In the knee joints of transgenic mice, Cathepsin K was found near sites of matrix destruction in articular chondrocytes, particularly in calcified cartilaginous matrix and proliferating cells. It indicted that cathepsin K played an important role in the pathogenesis of osteoarthritis. They also gave an explain that cathepsin K could digest cartilage matrix components, therefore, it was considered to contribute to the progression of osteoarthritic damage. Such studies have provided new clew for the development of treatments aimed at holding back cartilage degeneration.[53]
4. Inhibition of proteases related to OA

There is currently no disease-modifying OA drug available, and treatment is limited to symptomatic relief or surgical replacement of affected joints. There is thus considerable interest in developing effective treatments that can halt or reverse the progression of the disease.

4.1. Inhibition of sclerostin

Till date, it is well documented that SOST inhibition is effective for treatment of osteoporosis. Tanners group have performed the DNA aptamer selectively against sclerostin, and characterized DNA aptamer-sclerostin binding affinity.[67] Aptamers can be used for therapeutic purposes and have been investigated in major disease such as osteoarthritis and osteoporosis.[68]

There are several potential advantages of using aptamers for osteoarthritis and osteoporosis. Nucleic acids show good pharmacokinetic parameters in cartilage and joints, and many therapeutic targets tend to be extracellular so that the challenge of cross-membrane delivery of the nucleic acid can be avoided. Furthermore, aptamers also hold particular promise in conjunction with other technologies such as fluorescent nanoclusters which open up new possibilities for diagnostic imaging. At last the stable aptamers display effective and specific dose-dependent inhibition of sclerostin's antagonistic effect on Wnt activity. Their studies have provided an alternative approach to inhibit sclerostin function with therapeutic potential.

However, there is no pre-clinical or clinical evidence to show its efficacy for the treatment of osteoarthritis. Its role in OA treatment is still under premature. É. Abed et al. explored the role played by Sirtuin 1 and SOST on the abnormal mineralization and cWnt signaling in human osteoarthritic subchondral osteoblast (OA Ob). The results indicated that high level of SOST was responsible, in part for the reduced cWnt and mineralization of human OA Ob, which in turn is linked with abnormal SIRT1 levels in these pathological cells.[69] A recent study found that absence of sclerostin in mice with genetic knockout of sclerostin did not alter development of age-dependent osteoarthritis, and that anti-sclerostin therapy with a monoclonal antibody in rats with post-traumatic osteoarthritis had no effect on articular cartilage remodeling.[50] Anyway, antisclerostin therapy has appeared be a promising approach to the treatment of osteoporosis, while Wnt/β-catenin signaling has also been implicated in the pathogenesis of osteoarthritis, with the potential for therapeutic intervention yet to be determined.[70]

4.2. Inhibition of MMPs and ADAMTs

According to the reports, it is known that the MMPs can be effectively inhibited by TIMP-1, -2, -3, -4.[71] Similar to MMPs, ADAMTS family members can also be inhibited effectively by TIMPs.[72-73] It is illustrated that TIMP's is a significant candidate of blocking cartilage degradation. And of particular note is that TIMP-3 can inhibit several ADAM/ADAMTS proteinases, as reported in lots of existed literatures, while TIMP-1 shows ability to inhibit ADAMTS-10.[72-77] In addition, it is also reported that TIMP-3 can be endocytosed and degraded by chondrocytes,[78] suggesting that its activity in cartilage may be regulated post-translationally rather than transcriptionally.[10]
Wayne et al. have demonstrated that inhibition of full-length ADAMTS-4 by TIMP-3 was enhanced in the presence of aggregan, and this interaction was mediated largely through the binding of aggregan and the spacer domains of ADAMTS-4 to form a complex with an improved binding affinity for TIMP-3 over free ADAMTS-4. Therefore, the results also indicated that the cartilage environment could modulate the function of protease-inhibitor systems and have relevance for therapeutic approaches to aggreganase modulation.[79]

ADAMTS-2 is an activity necessary for the formation of extracellular matrix and responsible for cleaving the N-propeptides of procollagens I–III. Wang et al. have shown that TIMP-3 inhibited ADAMTS-2 in vitro with apparent $K_i$ values of 160 and 602 nM, in the presence of heparin or without respectively. In a word, TIMP-3 was shown to inhibit procollagen processing by cells.[80]

4.3. Inhibition of cathepsin K

Cathepsin K contains a highly conserved catalytic triad Cys25, His159, and Asn175 within its active site. And in design of the cathepsin K inhibitors, there are several key elements that need to be considered, its inhibitors must be reversible so as to prevent antigenicity arising from covalent modification of proteins via irreversible, such as aldehydes, ketones and nitriles. These reversible inhibitors have become more crucial in recent years because they combine strongly to the cathepsin K with low reactivity towards cellular nucleophiles.[81] In addition, the selectivity of inhibitors towards cathepsin K and other cysteine are also desirable to avoid side effects.[82]

4.3.1. Aldehydes and ketones

Aldehydes and ketones modulate cathepsin K activity via hemiacetal/thiohemiacetal and bond formation. Some representatives of aldehyde- and ketone-based reversible covalent cathepsin K inhibitors have reached stages of clinical trials.[83-84]

Since selectivity is important when designing potential drugs to avoid undesired toxicities, Boros et al. have obtained several of selective aldehyde-based inhibitors[85] and some of them presented at least 500-fold more potent for cathepsin K than cathepsin B or L. These results gave the encouragement that the aldehyde-based inhibitors could be developed as an anti-OA drug in targeting Cath K. In addition, cyclic ketone was also indicated as the inhibitors of the cysteine protease cathepsin K.

Crystallographic and structure-activity (SA) studies on acyclic ketone-based inhibitors of cathepsin K have guided the design and identification of two series of cyclic ketone inhibitors. Marquis et al. have found that the 3-amidopyrrolidin-4-one inhibitors were bound into the active site of the cathepsin K with two alternate directions. Epimerization issues associated with the labile alpha-amino ketone diastereomeric center contained within these inhibitor classes has proven to limit their utility.[86] The results showed that the heterogeneous ketone inhibitors have different influence on the practical application.
4.3.2. Nitriles

Inhibitors for papain-like cysteine are derived from peptides, they contain electrophilic group and have been shown to covalently interact with the thiol group at the active site of cathepsin K under formation a thioimidate adduct. Among many types of inhibitors, nitriles have received much attention in recent study.[87-88]

Three chemical classes of nitrile-containing inhibitors of cysteine proteases are known as: a) cyanamides,[89] b) aromatic nitriles,[90] and c) aza-nitrile derivatives, which includes a P1 aza-amino nitrile.[91-93] Among these inhibitors the aza-nitrile derivatives are the optimal ones due to the unique properties such as proteolytical stabilization, reversible binding and excellent inhibitory activity.[94]

In 2013, Ren and Yuan *et al* in our research group has synthesized two new series of cathepsin K inhibitors. The first series with P2-P3 amide linker have both high selectivity and potency, especially the meta-triaryl compound 13 is significantly more potent to cathepsin K (K<sub>i</sub> = 0.0031 nM). The second series without the P2-P3 amide linkage have showed a remarkable improvements, the triaryl *meta*-product 13′ possessed a favorable balance between potency (K<sub>i</sub> = 0.29 nM) and selectivity of cathepsin K over L, S, B (320-, 1784-, 8566-fold). Such a selective improvement would be useful to avoid harmful side effects in practical applications of the inhibitors.[94-95]

5. Conclusion and perspective

A significant improvement about scientific cognition of osteoarthritis have been achieved in the past decades, both the aggrecan and collagen play a supporting role in cartilage. It is indisputable that there is a close relationship between the component lost and cartilage degradation, and people are becoming increasingly aware that osteoarthritis is a serious joint disease which is adjusted by proteases and is performed as the degradation of the cartilage extracellular matrix. In addition, we also summarized the profoundly reorganizations that risk factors for OA contain obesity, sports injury, joint instability, particular muscle weakness, genetic, occupational factors and so on. These are related with mechanical, genetic, metabolic factors launch and hold the biochemical changes result the joint dysfunction.

As stated above, a wide range of work in the past years has proved that several proteases are intertwined with osteoarthritis and focused upon in clinical trials. Sclerostin, MMPs, ADAMTS, cathepsins and LDH have become key targets in the development of the diagnosis and treatment of osteoarthritis, and significant progress has been made over the decades. It is no doubt that international co-work in this area will made great progress in the near future and lead to some effective treatment methods in order to alleviate the symptoms and hamper the progression of osteoarthritis.
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