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Osteoarthritis Pathogenesis: A Review of Molecular Mechanisms

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Abstract

Osteoarthritis (OA), the most prevalent chronic joint disease, increases in prevalence with age, and affects majority of individuals over the age of 65 and is a leading musculoskeletal cause of impaired mobility in the elderly. Because the precise molecular mechanisms which are involved in the degradation of cartilage matrix and development of OA are poorly understood and there are currently no effective interventions to decelerate the progression of OA or retard the irreversible degradation of cartilage except for total joint replacement surgery. In this paper, the important molecular mechanisms related to OA pathogenesis will be summarized and new insights into potential molecular targets for the prevention and treatment of OA will be provided.

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Keywords

Osteoarthritis; Molecular mechanisms; Potential therapeutic approches

Introduction

Osteoarthritis (OA), the most prevalent chronic joint disease, increases in prevalence with age, and affects majority of individuals over the age of 65 [1, 2]. A report from the Third National Health and Nutrition Examination Survey reveals that about 37.4 % of adults in the United States who are 60 years of age or older have radiographic evidence of OA [3]. OA most affects the joint including knees, hands, hips, and spine, and is a leading musculoskeletal cause of impaired mobility in the elderly [4, 5]. While several risk factors associated with OA have been put forward, including genetic predisposition, aging, obesity, and joint mal-alignment, the pathogenesis of OA remains largely unclear [6, 7]. The major clinical symptoms include chronic pain, joint instability, stiffness, joint deformities, and radiographic joint space narrowing [8, 9]. Treatment of osteoarthritis involves alleviating pain, reducing stiffness, maintaining the functional capacities and improving quality of life [8]. Current treatments include low-impact aerobic exercise [10], weight loss [11], acupuncture [12], glucosamine and chondroitin Sulfate [13], and surgical [14]. Because the precise molecular mechanisms which involved in pathogenesis of OA are poorly understood and there are currently no effective interventions to decelerate the progression of OA or retard the irreversible degradation of cartilage except for total joint replacement surgery [15]. The economic burden of osteoarthritis may exceed $60 billion per year in the United States [16]. In this paper, the important molecular mechanisms related to OA pathogenesis will be summarized and new insights into potential molecular targets for the prevention and treatment of OA will be provided.

Characteristics of Articular Cartilage

Articular cartilage is mainly composed of tissue fluid, type II collagen (Col2), and proteoglycans. Of the wet mass, 65–80 % of cartilage is tissue fluid. This high fluid content enables nutrients and oxygen to diffuse through the cartilage matrix to its cells. Collagen type II, and proteoglycans account for 15–22 and 4–7 % of the cartilage wet weight, respectively [17]. Other collagens and proteoglycans such as types V, VI, IX, X, XI, XII, XIV collagens [18] and decorin, biglycan, fibromodulin, lumican, epiphycan, and perlecan [19] also account for a small part (less than 5 %) of the normal cartilage composition. The articular chondrocyte is the only cell type in articular cartilage and responsible for generating and maintaining the cartilaginous extracellular environment [20, 21].

The collagen/proteoglycan matrix consists of a highly dense meshwork of collagen fibrils including the major collagen type II (Col2) and minor collagen types IX, and XI embedded in gel-like negatively-charged proteoglycans [22]. This hydrated architecture of the matrix provides the articular cartilage with tensile and resilient strength which allows joints to maintain proper biomechanical function [23].

As articular cartilage matures, articular chondrocytes maintain the cartilage by synthesizing matrix components (Col2 and proteoglycans) and matrix degrading enzymes with minimal turnover of cells and matrix. The existing collagen network becomes cross-linked, and articular cartilage matures into a permanent tissue with the ability to absorb and respond to mechanical stress [24]. Under normal conditions, articular chondrocytes become arrested at a pre-hypertrophic stage of differentiation, thereby persisting throughout postnatal life to maintain normal articular cartilage structure [25].

Progression of OA

Articular cartilage can be damaged by normal wear and tear or pathological processes such as abnormal mechanical loading or injury. During the early stages of OA, the cartilage surface is still intact. The molecular composition and organization of the extracellular matrix is altered first [26]. The articular chondrocytes, which possess little regenerative capacity and have a low metabolic activity in normal joints, exhibit a transient proliferative response and increased matrix synthesis (Col2, aggrecan etc.) attempting to initiate repair causing by pathological stimulation. This response is characterized by chondrocyte cloning to form clusters and hypertrophic differentiation, including expression of hypertrophic markers such as Runx2, ColX, and Mmp13. Changes in the composition and structure of the articular cartilage further stimulate chondrocytes to produce more catabolic factors involved in cartilage degradation. As proteoglycans and then the collagen network breakdown [27], cartilage integrity is disrupted. The articular chondrocytes will then undergo apoptosis and the articular cartilage will eventually be completely lost. The reduced joint space resulting from total loss of cartilage will cause friction between bones, leading to pain and limited joint mobility. Other signs of OA, including subchondral sclerosis, bone eburnation, osteophyte formation, as well as loosening and weakness of muscles and tendons will also appear.

Molecular Mechanisms Related to OA Pathogenesis

The etiology of OA is multi-factorial, including genetic predisposition, aging, obesity, and joint mal-alignment and prior joint injury or surgery [6, 7], which can be segregated into categories such as mechanical influences, the effects of aging and genetic factors. Studies show that loss of intact meniscus function leads to OA in humans due to joint instability and abnormal mechanical loading [28, 29]. Recently, the meniscal ligamentous injury (MLI) induced-OA model is becoming a well established mouse model which mimics clinical situation allowing us to study the development and progression of trauma-induced OA on defined genetic backgrounds [30]. In this model, the ligation of the medial collateral ligament coupled with disruption of the meniscus from its anterior-medial attachment can reproducibly induce OA over a 3 month time period. There are rare cases of OA involving mutations of types II, IX, and XI collagen [31, 32]. In addition, there was precious little evidence that inflammatory cytokines such as prostaglandins, TNF-α, interleukin-1, interleukin-6 and nitric oxide, are important in vivo even though they are potent inducers in vitro [33]. It is well known that genetic factors contribute to the susceptibility for OA. Several studies have demonstrated that molecular mechanisms might be related to the pathogenesis of OA.

Growth Factors and OA

TGF-β—Chondrocyte differentiation and maturation during endochondral ossification are tightly regulated by several key growth factors and transcription factors, including members of the transforming growth factor β (TGF-β) super family, fibroblast growth factors (FGFs), Platelet-derived growth factor (PDGF),and parathyroid hormone-related protein (PTHrP) [34-38]. Growth factors have been extensively studied for pathogenesis of OA and cartilage repair because of its ability to enhance matrix synthesis [39].

Since TGF-β inhibits chondrocyte hypertrophy and maturation, the inhibition of TGF-β signaling represents a potential mechanism in the development of OA [40]. There are three isoforms of TGF-β, TGF-β1, 2 and 3, which can bind to the type II receptor to activate the canonical TGF-β/Smad signaling cascade. In the canonical pathway, TGF-β binds to the type II receptor which then phosphorylates type I transmembrane serine/threonine kinase receptors. The type I receptor subsequently phosphorylates Smads 2 and 3 (R-Smad) at a conserved SSXS motif at the C-terminus of Smads 2 and 3. The activated R-Smads thus dissociate from the receptor complex and form a heteromeric complex with the common Smad, Smad4. This heteromeric Smad complex then enters the nucleus and associates with other DNA binding proteins to regulate target gene transcription [41].

Loss of TGF-β signaling is associated with cartilage damage, which suggesting loss of the protective effect of TGF-β during osteoarthritis progression. Additionally, TGF-β is involved in early osteophyte formation [40]. In mice, targeted disruption of the TGF-β1 gene results in diffuse, and lethal inflammation about 3 weeks after birth and loss of TGF-β2 or TGF-β3 results in defects in bone development affecting the forelimbs, hindlimbs, and craniofacial bones, suggesting that TGF-β plays an important role in skeletogenesis [42].

Recent genetic manipulation of TGF-β signaling members also demonstrated that TGF-β signaling plays a critical role during OA development. Transgenic mice that over-express the dominant-negative type II TGF-β receptor (dnTgfbr2) in skeletal tissue exhibit articular chondrocyte hypertrophy with increased type X collagen expression, cartilage disorganization and progressive degradation [43]. Consistent with these findings, Smad3 knockout mice show progressive articular cartilage degradation resembling human OA [44]. In order to overcome embryonic lethality and redundancy, we generated chondrocyte-specific Tgfbr2 conditional knockout mice (Tgfbr2 cKO or Tgfbr2Col2CreER mice) in which deletion of the Tgfbr2 gene is mediated by Cre recombinase driven by the chondrocyte-specific Col2a1 promoter in a tamoxifen (TM)-inducible manner [45, 46]. These mice exhibit typical clinical features of OA, including cell cloning, chondrocyte hypertrophy, cartilage surface fibrillation, vertical clefts, and severe articular cartilage damage as well as the formation of chondrophytes and osteophytes [47]. In addition, the relationship between TGF-β and OA is strengthened by the discovery that a single nucleotide polymorphism (SNP) in the human Smad3 gene is linked to the incidence of hip and knee OA in a 527 patient cohort [48].

The TGF-β pathway has been identified as a key signaling pathway in osteoarthritis, but evidence for both protective and catabolic roles of TGF-β signaling has been reported. Zhen et al. provide new evidence using several models of osteoarthritis to show that TGF-β is

involved in aberrant bone remodeling and cartilage degeneration in osteoarthritis. As increased TGF-β activity in the subchondral bone can be a primary cause of osteoarthritis and can initiate pathology, therapeutic targeting may be used to prevent and ease the disease [49].

Loss of TGF-β signaling in cartilage induces chondrocyte hypertrophy, eventually leading to cartilage degeneration, and pharmacological activation of the TGF-β pathway has therefore been proposed to preserve articular cartilage integrity during osteoarthritis [50]. However, such a strategy exist several caveats, for example, TGF-β signaling in chondrocytes seems to switch from the canonical anabolic ALK5-Smad2/3 pathway to the catabolic ALK1-Smad1/5/8 pathway as they age, suggesting that TGF-β supplementation in aged individuals might actually exacerbate cartilage destruction [34].

FGF-2 and FGF-18—Some other growth factors have been described as having a role in the response of cartilage to injury and the development of OA [51]. Of these growth factors, the fibroblast growth factor (FGF) signaling family is known to have several roles [52, 53]. FGF-2 have a potent catabolic and anti-anabolic role in human cartilage homeostasis [54]. FGF-2 is released in supraphysiological amounts during loading and/or injury of the cartilage matrix and activates multiple transduction signal pathways (MAPKs), such as ERK, p38, and JNK [52]. FGF-2 could stimulate MMP-13 expression potently, which is the major degrading enzyme to type II collagen [55]. The FGFR1-Ras/PKCδ-Raf-MEK1/2-ERK1/2 signaling pathway is activated after FGF-2 stimulation, which mediates up-regulation of matrix-degrading enzyme expression (ADAMTS-5 and MMP-13), as well as down-regulation of aggrecan expression [54, 56-58]. Correspondingly, PKCδ inhibition significantly impairs these detrimental effects mediated by FGF-2. These findings provide deeper insights into the feasibility of utilizing downstream FGF-2 pathway-specific inhibitors in prevention and/or treatment of degenerative joint diseases. Future focuses may be toward elucidating pharmacological interventions that have a high translational potential and may establish the potential efficacy of a PKCδ peptide inhibitor in the treatment of OA [59].

FGF-18, a secreted heparin-binding polypeptide growth factor, has been shown to have a number of functions in different organs [60, 61]. In the musculoskeletal system, FGF-18 is involved in cartilage growth and maturation and is implicated in the development of functional cartilage and bone tissue [62, 63]. It is also involved in processes within mature cartilage [62, 63] as well as being shown to have a role in enhancing regeneration and repair [64, 65]. Studies have examined the effects of FGF-18 on damaged cartilage. For example, Moore et al. [65] has recently demonstrated that FGF-18 stimulated chondrogenesis and articular cartilage repair in mechanical damage models. And in an in vitro damage/repair model, rhFGF18 increases the proteoglycan synthesis, the repair cell number and prevents apoptosis [66, 67]. These results indicate that rhFGF18 may be a good candidate growth factor candidate for enhancement of cartilage repair following mechanical damage.

Wnt, β-Catenin and OA

The canonical Wnt/β-catenin signaling, which controls multiple developmental processes in skeletal and joint patterning, may also be involved in the progression of OA. When Wnt binds its receptor Frizzled and the co-receptor protein LRP5/6, the signaling protein Disheveled (Dsh) is activated, leading to inactivation of the serine/threonine kinase GSK-3β, thus inhibiting the ubiquitination and degradation of β-catenin. β-catenin then accumulates in the nucleus and binds LEF-1/TCF to regulate the expression of Wnt target genes. In the absence of the Wnt ligand, cytosolic β-catenin binds the APC-Axin-GSK-3β degradation complex, and GSK-3β in this complex phosphorylates β-catenin to induce its proteosomal degradation. The degradation of β-catenin represses the expression of Wnt responsive genes, allowing binding of the corepressor Groucho to the transcription factors LEF-1/TCF.

In vitro studies show that over-expression of constitutively active β-catenin leads to loss of the chondrocyte phenotype including reduced Sox9 and Col2 expression in chick chondrocytes [68]. Genome-wide scans, candidate gene association analyses and single nucleotide polymorphism (SNP) studies have demonstrated the association of hip OA with the Arg324Gly substitution mutation in the sFRP3 protein that antagonizes the binding of Wnt ligands to the Frizzled receptors. The mutation of sFRP3 causes increased levels of active β-catenin, promoting aberrant articular chondrocyte hypertrophy and thereby leading to hip and knee OA in patients [69-72]. Lories et al. [73] reported that the genetic association between osteoarthritis and FRZB polymorphisms is corroborated by increased cartilage proteoglycan loss in models of arthritis in Frzb(−/−) mice and loss of Frzb may contribute to cartilage damage by increasing the expression and activity of Mmps, in a Wnt-dependent and Wnt-independent manner. Consistent with this finding, Frzb knockout mice are more sensitive to chemical-induced OA [74].

Since human genetic association studies suggest that Wnt/β-catenin signaling may play a critical role in the pathogenesis of OA, we have generated chondrocyte-specific β-catenin conditional activation (cAct) mice. These mice show high expression of β-catenin in articular chondrocytes leading to abnormal articular chondrocyte maturation and progressive loss of the articular cartilage surface in 5- and 8-month old mice [75]. The role of Wnt/β-catenin signaling in cartilage degeneration is further demonstrated in other animal models. Chondrocyte-specific Col2a1-Smurf2 transgenic mice develop an OA-like phenotype due to up-regulation of β-catenin caused by Smurf2-induced ubiquitination and degradation of GSK-3β [76]. Furthermore, over-expression of Wnt-induced signaling protein 1 (WISP-1) in the mouse knee joint also leads to cartilage destruction [77]. Consistent with these findings, it has been reported that a panel of Wnt signaling related genes, including WISP-1 and β-catenin, was significantly up-regulated in knee joints and disc samples from patients with OA and disc degenerative disease [77]. However, some research reported that inhibition of β-catenin signaling in articular chondrocytes causes increased cell apoptosis and articular cartilage destruction in Col2a1-ICAT- transgenic mice [78].

The discovery of drugs exerting selective effects on the Wnt/β-catenin signaling may help to delimitate the specific roles of this pathway in cartilage degeneration and repair [79]. Recently, a number of antagonists have been identified as the small molecule XAV939, which selectively inhibits β-catenin-mediated transcription by stabilizing axin [80]. Elevated

circulating levels of Wnt inhibitor Dickkopf-1 (Dkk-1) are associated with reduced progression of radiologic hip OA in elderly women [81], however, inhibition of this agent results in the bone-forming pattern of OA in animals [82]. Further studies are needed to establish the role of the different components of the Wnt/β-catenin pathway and their interaction networks.

Indian Hedgehog (Ihh) and OA

The Ihh/parathyroid hormone-related protein (PTHrP) negative-feedback loop is critical for chondrocyte differentiation during endochondral bone formation. Articular chondrocytes undergo cellular changes reminiscent of terminal growth plate chondrocyte differentiation during OA [83]. These observations suggest Ihh signaling may play a pivotal role in OA development. Ihh is a major Hh ligand in chondrocytes, which binds with the Patched-1 (PTCH1) receptor to release its inhibition on Smoothened (SMO). SMO can then activate the glioma-associated oncogene homolog (Gli) family of transcription factors to initiate transcription of specific downstream target genes, including Ihh signaling pathway members Gli1, Ptch1 and hedgehog-interacting protein (HHIP).

Immunohistochemical studies demonstrated that Ihh signaling activation positively correlates with the severity of OA in human OA knee joint tissues and high expression of GLI1, PTCH, and HHIP was found in surgically induced murine OA articular cartilage. Activation of Ihh signaling in mice with chondrocyte-specific over-expression of the Gli2 or Smo genes induced a spontaneous OA-like phenotype with high MMP13, ADAMTS5, and ColX expression. In contrast, deletion of the Smo gene or treatment with a pharmacological inhibitor of Ihh attenuated the severity of OA induced by MLI injury [84].

Genetic studies using knockout mice showed that activation of Ihh downstream signaling pathways results in a decrease in articular cartilage thickness and proteoglycan content while inhibiting Ihh signaling results in an increase of articular cartilage thickness and PG [85, 86]. Consistent with these observations, upregulation of hedgehog (Hh) signaling in postnatal cartilage promotes chondrocyte hypertrophy and cartilage degradation [87], suggesting the possibility that blocking Ihh signaling can be used as a therapeutic approach to prevent or delay cartilage degeneration. However, Ihh gene deletion is currently not a therapeutic option as it is lethal in animals. RNA interference (RNAi) provides a means to knockdown Ihh without the severe side effects caused by chemical inhibitors [88]. In the future, it will be necessary to develop a safe and effective RNAi delivery system to target Ihh signaling for preventing and treating OA [89].

HIF-2α and OA

The HIF proteins, including HIF-1, 2 and 3, are the basic helix-loop-helix transcription factors which function differently under normoxic and hypoxic conditions [90-93]. HIF-1α, in the articular cartilage, acts as an anabolic signal by stimulating specific extracellular matrix synthesis [94,95]. In contrast, HIF-2α (encoded by EPAS1) is a potential catabolic regulator of articular cartilage and induces articular cartilage degeneration [96, 97]. Promoter assays suggest that NF-κB signaling could significantly induce HIF-2α expression and then HIF-2α specifically regulate transcription of several catabolic genes such as

Mmp13 [96]. Genetic screen using the human osteoarhritic cartilage UniGene library suggests that HIF-2α is a potential catabolic regulator of articular cartilage [97]. Based on the Japanese population ROAD study, a functional SNP in human EPAS1 proximal promoter region was associated with knee osteoarthritis in a 397 patient cohort [96, 98]. Consistent with this finding, HIF-2α expression was markedly increased in OA patients with degenerative cartilage [96, 97]. Chondrocyte-specific Epas1 transgenic mice could spontaneously develop osteoarthritis phenotype with increased MMP13 and ColX expression in articular cartilage. In addition, Epas1 heteozygous deficient mice showed resistance to cartilage degeneration induced by meniscus surgery [96, 97]. Therefore, HIF-2α may be a critical transcription factor that targets several genes for osteoarthritis development.

However, due to the absence of vasculature, the chondrocytes, the only cell type present in the tissue, are appear to have developed specific mechanisms to promote tissue function in response to chronic hypoxia, for example, by inducing increased expression of cartilage matrix components [99-101]. Hypoxia-inducible factors (HIFs) appear to be critical to tissue-specific responses in chondrocytes. Applying the technique of RNA interference, they subsequently demonstrated that HIF-2α was critical for this hypoxic induction of cartilage matrix synthesis in HACs [99]. Furthermore, the main matrix genes, such as those encoding Col-2a1, aggrecan and Col-9 are up-regulated by hypoxia through cartilage-specific transcription factor SOX9. When putative hypoxia response element sequences were mutated, hypoxic induction was abolished. In addition, the specific role of HIFs in this hypoxic induction of chondrogenesis from MSCs deserves further exploration, and interestingly, Hardingham and colleagues have recently shown that human MSCs isolated from the infrapatellar fat pad showed enhanced chondrogenic differentiation in hypoxia, and furthermore, that HIF-2α, but not HIF-1α, was up-regulated in these cultures [102].

However, HIF-2α is a potential therapeutic strategy for the regulation of osteoarthritic cartilage destruction, some caution seems warranted. Most transcription factors are active in multiple cell types and to avoid systemic side effects of a putative inhibitor, local targeting of OA affected joints probably is the preferred way forward [103]. In addition, HIF-2a is primarily expressed in early stages of OA, so therapy should be started at recent onset of OA [104].

GDF-5 and OA

Growth differentiation factor 5 (GDF-5), which is a member of TGF-β superfamily [105], is an extracellular signaling molecule that participates in bone and cartilage morphogenesis as well as in joint formation [106].

A number of studies have demonstrated that GDF-5 plays important roles in musculoskeletal processes, affecting endochondral ossification, synovial joint formation, tendon maintenance, and bone formation [107, 108]. Defects of this gene were shown to be correlated to abnormal joint development or skeletal disorders in humans and mice [109-112]. Mutations in human GDF-5 gene result in a broad spectrum of skeletal disorders [113]. Miyamoto et al. genotyped a number of common GDF-5 polymorphisms and demonstrated that rs143383, a T to C transition located in the 5′ untranslated region (5′UTR)

of the gene, was significantly associated with OA [114]. Further studies have revealed that rs143383 is functional, the OA-associated T-allele mediating reduced GDF-5 transcription relative to the C-allele in all of the joint tissues [115, 116], however, some other groups did not confirm these results [117].

Mouse models have provided a basis for better understanding of the role of GDF-5 in skeletogenesis and joint maintenance [109-111]. The brachypodism (bp) mice which carry a functional null allele of GDF-5 caused by a frame-shift mutation, exhibited abnormal skeletal and bone development [118, 119]. However, Gdf5Bp-J/+ mice appeared phenotypically normal, but do show an increased propensity of developing an OA phenotype when challenged [120]. This model suggested that decreased GDF-5 levels in mice contribute to osteoarthritis development. In addition, GDF-5 deficient mice exhibited biomechanical abnormalities in the tendon, which may be associated with altered type I collagen and skeletal abnormalities, one hypothesis of the mechanism behind that was GDF-5 might modulate the rate of endochondral bone growth by affecting the duration of the hypertrophic phase in growth plate chondrocytes [121]. It is supportive of the genetic data indicating the association between GDF-5 and human osteoarthritis, however, it remains unclear why the frequency of the associated alleles varies across studies, identification of functional variants will probably require biological as well as additional genetic assays.

Several studies have reported the use of GDF5 in therapeutics. Bobacz et al. [122] showed an increase in glycosaminoglycan (GAG) synthesis in normal and OA chondrocytes cultured with GDF5, and an increase in ACAN mRNA levels. Chubinskaya et al. [123] observed an increase in GAG synthesis in alginate bead cultures of chondrocytes in the presence of GDF5. However, Ratnayake et al. [124] showed that osteoarthritis chondrocytes do not respond in a predictable manner to culture with exogenous GDF5. This may be a cause or a consequence of the osteoarthritis disease process and will need to be surmounted if treatment with exogenous GDF5 is to be advanced as a potential means to overcome the genetic deficit conferring osteoarthritis susceptibility at this gene [124].

MMP-13, ADAMTS, and OA

MMP-13 is a substrate-specific enzyme that targets collagen for degradation. Compared to other MMPs, MMP-13 expression is more restricted to connective tissues [125-128]. MMP-13 preferentially cleaves Col2, which is most abundant in articular cartilage and in the nucleus pulposus, inner anulus fibrosus and cartilage endplate of the intervertebral disc. It also targets the degradation of other proteins in cartilage, such as aggrecan, types IV and IX collagen, gelatin, osteonectin and perlecan [129]. MMP-13 has a much higher catalytic velocity rate compared with other MMPs over Col2 and gelatin, making it the most potent peptidolytic enzyme among collagenases [130, 131].

Clinical investigations revealed that patients with articular cartilage destruction had high MMP-13 expression [132], suggesting increased MMP-13 may be the cause of cartilage degradation. Mmp13 deficient mice show no gross phenotypic abnormalities, and the only alteration is in growth plate architecture during early cartilage development [133, 134]. However, transgenic mice with cartilage-specific Mmp13-overexpressing develop

spontaneous articular cartilage destruction characterized by excessive cleavage of Col2 and loss of aggrecan [135].

In the above-mentioned Tgfbr2 cKO and β-catenin cAct mouse models, MMP-13 expression is significantly increased [47, 60]. These findings suggest that MMP-13 deficiency does not affect articular cartilage function during the postnatal and adult stages but abnormal up-regulation of MMP-13 can lead to cartilage destruction. Moreover, deletion of the Mmp-13 gene prevents articular cartilage erosion induced by meniscal injury [136].

The ADAMTS family consists of large family members and they share several distinct protein modules as well. Studies show that ADAMTS 4 and 5 expression levels are significantly increased during OA development. Single knockout of the Adamts5 gene or double knockout of the Adamts4 and Adamts5 genes prevents cartilage degradation in surgery-induced and chemical-induced murine knee OA models [137-139]. Interestingly, in Tgfbr2 cKO, β-catenin and Ihh activation mouse models, ADAMTS5 was significantly increased in articular cartilage tissue, suggesting that maintaining proper ADAMTS5 levels are essential for normal articular cartilage function. Taken together, these findings indicate that catabolic enzymes play a significant role in OA progression and targeting these enzymes may be a viable therapeutic strategy to decelerate articular cartilage degradation.

Since MMP-13 and ADAMTS5 are two potentially attractive targets for OA therapy, the inhibition of these enzymes and their regulatory mechanisms has been extensively studied. Tissue inhibitors of metalloproteinases (TIMP) are specific inhibitors which directly bind MMPs and ADAMTS in chondrocytes to prevent the destruction of articular cartilage [140]. A specific small molecule MMP-13 inhibitor can attenuate the severity of OA in the MLI-induced injury model as well [141].

In addition to proteinase inhibitors, the transcription factor Runt domain factor-2 (Runx2) appears to be another potential target to regulate MMP-13 and ADAMTS5 in vivo. DNA sequence analysis of Mmp-13 and Adamts5 promoters identified putative Runx2 binding sites in the promoter regions of these genes. In addition, Runx2 has an overlapping expression pattern with MMP-13 and ADAMTS5, almost exclusively in the developing cartilage and bone, suggesting that Runx2 may be an important transcription factor regulating tissue-specific expression of Mmp13 and Adamts5 in articular chondrocytes [142-144]. Thus, manipulation of Runx2 expression in vivo could be an effective therapeutic strategy. During bone development, the temporal and spatial expression patterns of Runx2 are regulated by cytokines and growth factors including TGF-β, BMP, and FGF [145-148]. In addition to gene expression, Runx2 protein levels are also regulated through post-translational mechanisms involving phosphorylation, ubiquitination, and acetylation [149-154]. MicroRNA regulation is another important regulatory mechanism for protein translation. MicroRNA-140 (miR-140) is the first microRNA demonstrated to be involved in the pathogenesis of OA at least partially through regulation of ADAMTS5 mRNA expression. MiR-140 knockout mice are susceptible to age-related OA progression and conversely, over-expression of miR-140 in chondrocytes protects mice from OA development [155-157].

Summary

Articular chondrocyte is the sensor of articular cartilage homeostasis, and plays a critical role in maintaining the normal physiological structure and function of articular cartilage. Recent studies demonstrate that articular chondrocyte homeostasis can be disrupted by multiple factors, including abnormal mechanical loading, and aging. Additionally, genetic alterations in TGF-β/Smad, Wnt/β-catenin and Ihh signaling pathways can disrupt the balance between anabolic and catabolic activity in articular cartilage and result in irreversible degradation of the extracellular matrix. Thus far, most of the mouse models of osteoarthritis converge at the up-regulation of catabolic enzymes, such as MMP-13 and ADAMTS5, suggesting that these enzymes may serve as potential therapeutic targets in regulation of the progression of OA. In addition, manipulation of the above-mentioned molecule in articular chondrocytes could also play a role in articular cartilage regeneration.

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