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OSTEOARTHRITIS: INVESTIGATING MOLECULAR PATHOGENESIS MECHANISMS-REVIEW ARTICLE

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ABSTRACT

Background: Osteoarthritis (OA) is the most prevalent chronic joint disorder, particularly affecting individuals aged 65 and older. With rising incidence and substantial socioeconomic impact, it remains a significant challenge in geriatric healthcare. OA is characterized by chronic pain, stiffness, and reduced mobility, with current treatment options primarily focusing on symptomatic relief rather than addressing underlying pathophysiological mechanisms. **Aim:** This review aims to elucidate the molecular mechanisms underpinning OA pathogenesis, thereby highlighting potential therapeutic targets for prevention and treatment. **Methods:** A comprehensive literature review was conducted, encompassing recent studies on the cellular and molecular biology of articular cartilage, the role of growth factors, genetic predispositions, and mechanical stressors in OA development. **Results:** The findings reveal that articular cartilage undergoes significant structural and compositional changes during OA progression. Key molecular players include transforming growth factor-beta (TGF-β), which influences chondrocyte behavior and matrix composition, and various inflammatory cytokines that exacerbate cartilage degradation. Genetic factors and prior joint injuries also contribute to OA susceptibility and progression. **Conclusion:** Understanding the molecular pathogenesis of OA offers insights into novel therapeutic strategies aimed at altering disease progression. Targeting specific molecular pathways, particularly those involving TGF-β and associated signaling mechanisms, presents an opportunity for the development of effective interventions to preserve joint health.

KEYWORDS: Osteoarthritis, molecular mechanisms, TGF-β, chondrocytes, cartilage degradation, therapeutic targets.

INTRODUCTION

Osteoarthritis (OA), recognized as the most common chronic joint condition, demonstrates an increasing prevalence with advancing age, significantly impacting the majority of individuals aged 65 and above.[1,2] According to findings from the Third National Health and Nutrition Examination Survey, approximately 37.4% of adults in the United States aged 60 years or older exhibit radiographic indications of OA.[3] OA primarily affects joints such as the knees, hands, hips, and spine, serving as a leading musculoskeletal contributor to reduced mobility among the elderly population.[4,5] Numerous risk factors have been proposed in relation to OA, including genetic susceptibility, aging, obesity, and joint misalignment; however, the underlying mechanisms of OA pathogenesis remain largely elusive.[6,7] The principal clinical manifestations encompass chronic pain, joint instability, stiffness, joint deformities, and radiographic narrowing of joint space.[8,9] Management of osteoarthritis focuses on pain relief, stiffness reduction, functional capacity preservation, and quality of life enhancement.[8] Current therapeutic approaches include low-impact aerobic exercise,[10] weight reduction,[11] acupuncture,[12] glucosamine and chondroitin sulfate supplementation,[13] and surgical interventions.[14] Given that the specific molecular mechanisms implicated in OA pathogenesis are not well understood and there are currently no effective strategies to slow the progression of OA or prevent the irreversible deterioration of cartilage—other than total joint replacement surgery[15] the economic impact of osteoarthritis is estimated to exceed $60 billion annually in the United States.[16] This paper aims to summarize the critical molecular mechanisms associated with OA pathogenesis and offer new perspectives on potential molecular targets for the prevention and treatment of OA.

Characteristics of articular cartilage

Articular cartilage predominantly comprises tissue fluid, type II collagen (Col2), and proteoglycans. Notably, tissue fluid constitutes approximately 65–80% of the wet

mass of cartilage. This elevated fluid content facilitates the diffusion of nutrients and oxygen through the cartilage matrix to reach the resident cells. Type II collagen and proteoglycans make up about 15–22% and 4–7% of the wet weight of cartilage, respectively.[17] Additionally, other types of collagen (such as types V, VI, IX, X, XI, XII, and XIV)[18] and proteoglycans (including decorin, biglycan, fibromodulin, lumican, epiphycan, and perlecan)[19] contribute to less than 5% of the normal cartilage composition. The sole cell type within articular cartilage, the articular chondrocyte, is responsible for the synthesis and maintenance of the extracellular matrix.[20,21] The collagen/proteoglycan matrix features a highly dense network of collagen fibrils, predominantly composed of type II collagen (Col2) along with minor collagen types IX and XI, all embedded in gel-like, negatively charged proteoglycans.[22] This hydrated matrix architecture endows articular cartilage with tensile strength and resilience, essential for maintaining optimal biomechanical function in joints.[23]

As articular cartilage matures, chondrocytes sustain the tissue by producing matrix components (Col2 and proteoglycans) and matrix-degrading enzymes, with minimal turnover of both cells and matrix. The existing collagen network undergoes cross-linking, leading to the maturation of articular cartilage into a stable tissue capable of absorbing and responding to mechanical stress.[24] Under physiological conditions, articular chondrocytes typically remain in a pre-hypertrophic stage of differentiation, allowing them to persist throughout postnatal life and uphold the normal structural integrity of articular cartilage.[25]

Progression of osteoarthritis

Articular cartilage can sustain damage due to both routine wear and tear and pathological processes, including abnormal mechanical loading or injury. In the initial phases of osteoarthritis (OA), the cartilage surface remains intact, but the molecular composition and organization of the extracellular matrix undergo alterations first.[26] Articular chondrocytes, which possess limited regenerative capacity and exhibit low metabolic activity in healthy joints, display a transient proliferative response and an increase in matrix synthesis (including Col2 and aggrecan) in an effort to initiate repair prompted by pathological stimuli. This response is characterized by the cloning of chondrocytes, forming clusters and undergoing hypertrophic differentiation, which includes the expression of hypertrophic markers such as Runx2, ColX, and Mmp13. Further modifications in the composition and structure of articular cartilage stimulate chondrocytes to produce additional catabolic factors involved in cartilage degradation. As proteoglycans and the collagen network degrade,[27] cartilage integrity is compromised. Subsequently, the articular chondrocytes undergo apoptosis, ultimately resulting in the complete loss of articular cartilage. The consequent reduction in joint space due to total cartilage loss leads to friction between bones, causing pain and restricted joint mobility. Additional OA manifestations, including subchondral sclerosis, bone eburnation, osteophyte formation, as well as muscle and tendon loosening and weakness, will also emerge.

Molecular mechanisms related to oa pathogenesis

The etiology of OA is multifactorial, encompassing genetic predisposition, aging, obesity, joint malalignment, and prior joint injuries or surgeries.[6,7] These factors can be categorized into mechanical influences, aging effects, and genetic factors. Research indicates that the loss of intact meniscus function contributes to OA in humans due to joint instability and abnormal mechanical loading.[28,29] Recently, the meniscal ligamentous injury (MLI)-induced OA model has become an established murine model that accurately mimics clinical scenarios, facilitating the study of trauma-induced OA development and progression within defined genetic backgrounds.[30] In this model, ligation of the medial collateral ligament, along with disruption of the meniscus from its anterior-medial attachment, can reproducibly induce OA over a three-month period.

There are infrequent cases of OA associated with mutations in types II, IX, and XI collagen.[31,32] Furthermore, there is limited evidence to suggest that inflammatory cytokines—such as prostaglandins, TNF-α, interleukin-1, interleukin-6, and nitric oxide—play significant roles in vivo, despite being potent inducers in vitro.[33] It is well established that genetic factors influence susceptibility to OA, and various studies have indicated that specific molecular mechanisms may be implicated in OA pathogenesis.

Growth Factors and Osteoarthritis

TGF-β

Chondrocyte differentiation and maturation during endochondral ossification are tightly regulated by various key growth factors and transcription factors, including members of the transforming growth factor β (TGF-β) superfamily, fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and parathyroid hormone-related protein (PTHrP).[34–38] Growth factors have been extensively studied for their role in the pathogenesis of osteoarthritis (OA) and cartilage repair due to their capacity to enhance matrix synthesis.[39]

TGF-β plays a crucial role in the regulation of chondrocyte hypertrophy and maturation. The inhibition of TGF-β signaling may represent a potential mechanism in OA development.[40] There are three isoforms of TGF-β: TGF-β1, TGF-β2, and TGF-β3, which bind to the type II receptor to activate the canonical TGF-β/Smad signaling cascade. In this canonical pathway, TGF-β binds to the type II receptor, leading to the phosphorylation of type I transmembrane serine/threonine kinase receptors. The activated type I receptor subsequently phosphorylates Smads 2 and 3 (R-

Smads) at a conserved SSXS motif at their C-terminus. Once activated, R-Smads dissociate from the receptor complex and form a heteromeric complex with the common Smad, Smad4. This heteromeric Smad complex then translocates to the nucleus, where it associates with other DNA-binding proteins to regulate the transcription of target genes.[41]

Loss of TGF-β signaling has been associated with cartilage damage, suggesting that the protective effects of TGF-β are diminished during OA progression. Additionally, TGF-β is implicated in early osteophyte formation.[40] In mice, targeted disruption of the TGF-β1 gene leads to diffuse and lethal inflammation around three weeks after birth, while the loss of TGF-β2 or TGF-β3 results in skeletal defects affecting the forelimbs, hindlimbs, and craniofacial bones, indicating the essential role of TGF-β in skeletogenesis.[42]

Recent genetic manipulation of TGF-β signaling components further illustrates the critical role of TGF-β during OA development. Transgenic mice that overexpress the dominant-negative type II TGF-β receptor (dnTgfbr2) in skeletal tissues show articular chondrocyte hypertrophy with increased type X collagen expression, cartilage disorganization, and progressive degradation.[43] Similarly, Smad3 knockout mice exhibit progressive articular cartilage degradation resembling human OA.[44] To address embryonic lethality and redundancy, chondrocyte-specific Tgfbr2 conditional knockout mice (Tgfbr2 cKO or Tgfbr2Col2CreER mice) were generated, where the deletion of the Tgfbr2 gene is mediated by Cre recombinase driven by the chondrocyte-specific Col2a1 promoter in a tamoxifen-inducible manner.[45,46] These mice exhibit typical OA clinical features, including cell cloning, chondrocyte hypertrophy, cartilage surface fibrillation, vertical clefts, and severe articular cartilage damage, along with the formation of chondrophytes and osteophytes.[47] The relationship between TGF-β and OA is further supported 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 cohort of 527 patients.[48]

The TGF-β pathway is recognized as a key signaling pathway in osteoarthritis; however, evidence exists for both protective and catabolic roles of TGF-β signaling. Zhen et al. provided new evidence using various OA models, demonstrating that TGF-β is involved in aberrant bone remodeling and cartilage degeneration in OA. Increased TGF-β activity in the subchondral bone may be a primary cause of OA, initiating pathology and suggesting that therapeutic targeting of this pathway could help prevent or alleviate the disease.[49] Loss of TGF-β signaling in cartilage induces chondrocyte hypertrophy, ultimately leading to cartilage degeneration. Consequently, pharmacological activation of the TGF-β pathway has been proposed as a strategy to preserve articular cartilage integrity during osteoarthritis.[50] However, this strategy has several caveats; for instance, TGF-β signaling in chondrocytes appears to switch from the anabolic ALK5-Smad2/3 pathway to the catabolic ALK1-Smad1/5/8 pathway with aging, indicating that TGF-β supplementation in older individuals could potentially exacerbate cartilage destruction.[34]

Growth Factors and Osteoarthritis (OA)

Transforming Growth Factor Beta (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) superfamily, fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), and parathyroid hormone-related protein (PTHrP).[34–38] Growth factors have been extensively studied for their role in the pathogenesis of OA and cartilage repair due to their ability to enhance matrix synthesis.[39] TGF-β inhibits chondrocyte hypertrophy and maturation, suggesting that TGF-β signaling inhibition may contribute to OA development.[40] The TGF-β superfamily includes three isoforms: TGF-β1, TGF-β2, and TGF-β3, which bind to type II receptors to activate the canonical TGF-β/Smad signaling pathway. In this pathway, TGF-β binding to the type II receptor phosphorylates type I transmembrane serine/threonine kinase receptors. This phosphorylation activates Smads 2 and 3 (R-Smad), leading to their dissociation from the receptor complex and formation of a heteromeric complex with Smad4. This complex then translocates to the nucleus to regulate target gene transcription.[41]

Loss of TGF-β signaling is associated with cartilage damage, indicating the loss of its protective effects during OA progression. Additionally, TGF-β is implicated in early osteophyte formation.[40] In experimental models, targeted disruption of the TGF-β1 gene in mice leads to severe inflammation and skeletal defects, underscoring TGF-β's essential role in skeletogenesis.[42] Recent genetic manipulations of TGF-β signaling have revealed its critical role in OA. For example, transgenic mice that over-express a dominant-negative type II TGF-β receptor exhibit articular chondrocyte hypertrophy, cartilage disorganization, and progressive degradation.[43] Similarly, Smad3 knockout mice show progressive cartilage degradation that resembles human OA.[44] Conditional knockout mice with chondrocyte-specific deletion of TGF-β receptor 2 demonstrate clinical features of OA, such as chondrocyte hypertrophy and severe cartilage damage, further reinforcing the connection between TGF-β signaling and OA.[45–47] Notably, a single nucleotide polymorphism in the human Smad3 gene has been associated with hip and knee OA incidence.[48] The TGF-β pathway is recognized as pivotal in OA, but it exhibits both protective and catabolic roles. Research indicates that increased TGF-β activity in the subchondral bone may initiate OA pathology, suggesting that targeting this pathway could offer therapeutic opportunities.[49] Loss of TGF-β

signaling promotes chondrocyte hypertrophy and cartilage degeneration, leading to the proposal that pharmacological activation of TGF-β signaling may help maintain articular cartilage integrity in OA.[50] However, age-related signaling shifts from anabolic to catabolic pathways in chondrocytes complicate this strategy, potentially exacerbating cartilage destruction in older individuals.[34]

Fibroblast Growth Factor (FGF-2 and FGF-18)

Several other growth factors, including the fibroblast growth factor (FGF) signaling family, play critical roles in cartilage response to injury and OA development.[51] FGF-2, in particular, has been identified as having significant catabolic and anti-anabolic effects on human cartilage homeostasis.[54] FGF-2 is released in high amounts during cartilage loading or injury, activating various signal transduction pathways (MAPKs), such as ERK, p38, and JNK.[52] It can potently stimulate MMP-13 expression, a major enzyme degrading type II collagen.[55] Upon FGF-2 stimulation, the FGFR1-Ras/PKCδ-Raf-MEK1/2-ERK1/2 pathway is activated, leading to the up-regulation of matrix-degrading enzymes (ADAMTS-5 and MMP-13) and down-regulation of aggrecan expression.[54,56–58] Notably, inhibiting PKCδ significantly reduces the detrimental effects induced by FGF-2, indicating the potential for developing specific inhibitors targeting this pathway to prevent or treat degenerative joint diseases.[59]

FGF-18, another member of the FGF family, is crucial for cartilage growth, maturation, and functional tissue development in the musculoskeletal system.[60,61] It has shown promise in enhancing cartilage regeneration and repair. Studies by Moore et al. demonstrate that FGF-18 can stimulate chondrogenesis and repair damaged articular cartilage, enhancing proteoglycan synthesis and preventing apoptosis in in vitro models.[65,66,67] This positions rhFGF18 as a strong candidate for therapeutic applications in cartilage repair after mechanical injuries.

Wnt/β-Catenin Signaling and OA

The canonical Wnt/β-catenin signaling pathway plays a significant role in OA progression, regulating various developmental processes in skeletal and joint patterning. Wnt binds to its receptor, Frizzled, and co-receptor LRP5/6, activating Disheveled (Dsh) and inhibiting GSK-3β, leading to β-catenin stabilization. Accumulated β-catenin translocates to the nucleus, where it binds to LEF-1/TCF to regulate target gene expression. In the absence of Wnt, β-catenin is degraded, preventing the expression of Wnt-responsive genes.[68] In vitro studies indicate that over-expression of constitutively active β-catenin results in loss of chondrocyte phenotype, characterized by decreased Sox9 and Col2 expression.[68] Genetic studies have linked variants in the sFRP3 protein, which antagonizes Wnt binding, to hip OA, demonstrating how increased β-catenin levels contribute to aberrant articular chondrocyte hypertrophy.[69–72] Lories et al. showed that Frzb polymorphisms correlate with increased cartilage proteoglycan loss, highlighting Frzb's role in OA pathology.[73] Frzb knockout mice exhibit greater susceptibility to chemically-induced OA.[74]

Given the association of Wnt/β-catenin signaling with OA, researchers have developed chondrocyte-specific β-catenin conditional activation (cAct) mice, which show elevated β-catenin expression and progressive cartilage degradation.[75] Additional models further demonstrate that dysregulated β-catenin leads to cartilage degeneration.[76] Conversely, inhibiting β-catenin can increase chondrocyte apoptosis and cartilage destruction, complicating the therapeutic targeting of this pathway.[78] Selective inhibitors of Wnt/β-catenin signaling, such as XAV939, have emerged, showing promise in delineating the roles of this pathway in cartilage degeneration and repair.[79,80] Elevated levels of Wnt inhibitor Dickkopf-1 (Dkk-1) correlate with reduced hip OA progression in elderly women, though its inhibition can provoke a bone-forming OA phenotype.[81,82] Future research is needed to clarify the roles of Wnt signaling components and their interactions in OA pathology.

Indian Hedgehog (Ihh) and Hypoxia-Inducible Factor 2 Alpha (HIF-2α) in Osteoarthritis (OA)

Indian Hedgehog (Ihh) and OA

The negative-feedback loop involving Ihh and parathyroid hormone-related protein (PTHrP) is essential for the differentiation of chondrocytes during endochondral bone development. Articular chondrocytes exhibit cellular transformations analogous to those seen in terminal growth plate chondrocyte differentiation in the context of OA.[83] These findings imply that Ihh signaling could be crucial in the pathogenesis of OA. Ihh functions as a principal Hedgehog ligand in chondrocytes, binding to the Patched-1 (PTCH1) receptor to relieve its inhibitory effect on Smoothened (SMO). Subsequently, SMO activates the glioma-associated oncogene homolog (Gli) transcription factor family, initiating the transcription of specific downstream target genes, which include members of the Ihh signaling pathway such as Gli1, Ptch1, and hedgehog-interacting protein (HHIP).

Immunohistochemical investigations have revealed a positive correlation between Ihh signaling activation and the severity of OA in human knee joint tissues affected by OA, alongside heightened expression levels of GLI1, PTCH, and HHIP in surgically induced murine OA articular cartilage. In mice engineered to overexpress Gli2 or Smo specifically in chondrocytes, Ihh signaling activation led to the emergence of an OA-like phenotype characterized by elevated MMP13, ADAMTS5, and ColX levels. Conversely, deletion of the Smo gene or administration of a pharmacological Ihh inhibitor resulted in a reduction of OA severity induced by meniscal injury.[84]

Genetic analyses utilizing knockout mice demonstrated that the activation of Ihh downstream signaling pathways leads to a reduction in both the thickness of articular cartilage and the content of proteoglycans. In contrast, the inhibition of Ihh signaling was associated with an increase in cartilage thickness and proteoglycan levels.[85,86] These observations are in line with findings that the upregulation of hedgehog (Hh) signaling in postnatal cartilage fosters chondrocyte hypertrophy and the degradation of cartilage.[87] This indicates the potential for therapeutic strategies that target Ihh signaling to prevent or mitigate cartilage degeneration. However, the deletion of the Ihh gene is not a viable therapeutic approach, as it is lethal in animal models. RNA interference (RNAi) offers a method for downregulating Ihh without the severe adverse effects associated with chemical inhibitors.[88] Future research must focus on developing a safe and efficient RNAi delivery system to modulate Ihh signaling for the prevention and treatment of OA.[89]

HIF-2α and OA

Hypoxia-inducible factors (HIFs), including HIF-1, HIF-2, and HIF-3, are basic helix-loop-helix transcription factors that operate differently in normoxic versus hypoxic conditions.[90–93] HIF-1α serves as an anabolic signal within articular cartilage by stimulating the synthesis of specific extracellular matrix components.[94,95] In contrast, HIF-2α (encoded by EPAS1) acts as a potential catabolic regulator of articular cartilage, promoting its degeneration.[96,97] Promoter assays indicate that NF-κB signaling may significantly enhance HIF-2α expression, which subsequently regulates the transcription of several catabolic genes, including Mmp13.[96] Genetic screening utilizing the human osteoarthritic cartilage UniGene library suggests that HIF-2α may serve as a catabolic regulator of articular cartilage.[97] According to the Japanese ROAD study, a functional SNP in the proximal promoter region of human EPAS1 was linked to knee osteoarthritis in a cohort of 397 patients.[96,98] Supporting this, increased expression of HIF-2α was noted in OA patients exhibiting degenerative cartilage.[96,97] Transgenic mice with chondrocyte-specific Epas1 expression displayed spontaneous development of an osteoarthritis phenotype, characterized by elevated MMP13 and ColX expression within articular cartilage. Moreover, Epas1 heterozygous deficient mice demonstrated resistance to cartilage degeneration following meniscus surgery.[96,97] Therefore, HIF-2α appears to be a crucial transcription factor that targets various genes involved in the development of osteoarthritis.

Nevertheless, the absence of vascularization in cartilage indicates that chondrocytes, the sole cell type present in this tissue, have likely evolved specific mechanisms to maintain tissue function in response to chronic hypoxia, such as enhancing the expression of cartilage matrix components.[99–101] HIFs are critical for tissue-specific responses in chondrocytes. Utilizing RNA interference techniques, researchers have shown that HIF-2α plays a vital role in the hypoxic induction of cartilage matrix synthesis in human articular chondrocytes (HACs).[99] Additionally, key matrix genes like Col2a1, aggrecan, and Col9 are upregulated by hypoxia through the cartilage-specific transcription factor SOX9. Mutation of the hypoxia response element sequences negates this hypoxic induction. The specific contributions of HIFs to hypoxic chondrogenesis from mesenchymal stem cells (MSCs) merit further investigation. Interestingly, research by Hardingham and colleagues has indicated that human MSCs isolated from the infrapatellar fat pad exhibit enhanced chondrogenic differentiation under hypoxic conditions, with HIF-2α, rather than HIF-1α, being significantly upregulated in these cultures.[102]

While HIF-2α presents a promising therapeutic target for the modulation of osteoarthritic cartilage degradation, caution is advisable. Many transcription factors function across various cell types, necessitating the localized targeting of OA-affected joints to avoid systemic side effects associated with potential inhibitors.[103] Furthermore, since HIF-2α expression is predominantly observed in the early stages of OA, therapeutic interventions should be initiated promptly upon the onset of OA symptoms.[104]

Growth Differentiation Factor 5 (GDF-5) and Osteoarthritis (OA)

Growth differentiation factor 5 (GDF-5), a member of the TGF-β superfamily, functions as an extracellular signaling molecule integral to bone and cartilage morphogenesis as well as joint formation.[105,106] Numerous studies have elucidated the critical roles of GDF-5 in various musculoskeletal processes, including endochondral ossification, synovial joint formation, tendon maintenance, and bone development.[107,108] Genetic defects in GDF-5 have been correlated with abnormal joint development and skeletal disorders in both humans and murine models.[109–112] Specifically, mutations in the human GDF-5 gene are associated with a spectrum of skeletal anomalies.[113]

Miyamoto et al. identified significant associations between common GDF-5 polymorphisms and OA, particularly highlighting the rs143383 variant, a T to C transition located in the 5′ untranslated region (5′UTR) of the gene.[114] Further investigations have confirmed the functional relevance of rs143383, with the OA-associated T-allele exhibiting reduced GDF-5 transcription relative to the C-allele across various joint tissues.[115,116] however, these findings have not been universally corroborated.[117] Mouse models have significantly advanced the understanding of GDF-5's role in skeletogenesis and joint maintenance. For instance, brachypodism (bp) mice, which harbor a functional null allele of GDF-5 due to a frame-shift mutation, exhibit marked abnormalities in skeletal and bone development.[118,119] Conversely, Gdf5Bp-J/+ mice appear phenotypically normal yet display a heightened

propensity for developing OA when subjected to stressors.[120] These observations suggest that diminished GDF-5 levels in murine models contribute to OA pathogenesis. Additionally, GDF-5 deficiency in mice leads to biomechanical abnormalities in tendons, potentially due to alterations in type I collagen. One hypothesis posits that GDF-5 modulates the rate of endochondral bone growth by influencing the duration of the hypertrophic phase in growth plate chondrocytes.[121] While these findings substantiate the genetic correlation between GDF-5 and human OA, the variability in the frequency of associated alleles across different studies necessitates further exploration to identify functional variants through both biological and genetic assays.

Several investigations have explored the therapeutic potential of GDF-5. Bobacz et al. demonstrated an increase in glycosaminoglycan (GAG) synthesis in both normal and OA chondrocytes exposed to GDF-5, as evidenced by elevated ACAN mRNA levels.[122] Similarly, Chubinskaya et al. reported increased GAG synthesis in alginate bead cultures of chondrocytes in the presence of GDF-5.[123] However, Ratnayake et al. found that OA chondrocytes do not consistently respond predictably to exogenous GDF-5 treatment, suggesting that this variability may either stem from or contribute to the OA disease process.[124] Addressing this unpredictability will be crucial for advancing GDF-5 as a potential therapeutic option to mitigate the genetic predispositions conferring OA susceptibility linked to this gene.[124]

Matrix Metalloproteinase-13 (MMP-13), ADAMTS, and Osteoarthritis (OA)

Matrix metalloproteinase-13 (MMP-13) is a substrate-specific enzyme that predominantly targets collagen for degradation. In comparison to other matrix metalloproteinases (MMPs), MMP-13 expression is notably confined to connective tissues.[125–128] MMP-13 preferentially cleaves collagen type II (Col2), the most abundant protein in articular cartilage, as well as in other structures such as the nucleus pulposus, inner anulus fibrosus, and cartilage endplate of the intervertebral disc. This enzyme is also involved in the degradation of additional proteins in cartilage, including aggrecan, types IV and IX collagen, gelatin, osteonectin, and perlecan.[129] MMP-13 is characterized by a markedly higher catalytic velocity over Col2 and gelatin compared to other MMPs, establishing it as the most potent peptidolytic enzyme among collagenases.[130,131]

Clinical investigations have identified elevated MMP-13 expression in patients exhibiting articular cartilage destruction, suggesting a direct relationship between increased MMP-13 levels and cartilage degradation.[132] Mmp13-deficient mice demonstrate no significant gross phenotypic abnormalities; the only observed alteration occurs in the architecture of the growth plate during early cartilage development.[133,134] Conversely, transgenic mice with cartilage-specific overexpression of Mmp13 exhibit spontaneous articular cartilage destruction characterized by excessive Col2 cleavage and loss of aggrecan.[135] In Tgfbr2 conditional knockout (cKO) and β-catenin conditional activation mouse models, MMP-13 expression is significantly upregulated.[47-60] These findings suggest that MMP-13 deficiency does not impair articular cartilage function during postnatal and adult stages; however, aberrant upregulation of MMP-13 is associated with cartilage degradation. Notably, deletion of the Mmp-13 gene has been shown to prevent articular cartilage erosion induced by meniscal injury.[136]

The ADAMTS family consists of several large family members sharing distinct protein modules. Research indicates that expression levels of ADAMTS4 and ADAMTS5 significantly increase during OA development. Single knockout of the Adamts5 gene or double knockout of Adamts4 and Adamts5 genes effectively prevents cartilage degradation in both surgery-induced and chemical-induced murine knee OA models.[137–139] In Tgfbr2 cKO, β-catenin, and Indian hedgehog (Ihh) activation mouse models, elevated ADAMTS5 levels are observed in articular cartilage tissue, underscoring the necessity of maintaining appropriate ADAMTS5 levels for normal articular cartilage function. Collectively, these findings highlight the significant roles of catabolic enzymes in OA progression, suggesting that targeting these enzymes may constitute a viable therapeutic strategy for decelerating articular cartilage degradation. Given the potential of MMP-13 and ADAMTS5 as targets for OA therapy, extensive studies have focused on their inhibition and regulatory mechanisms. Tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors that directly bind to MMPs and ADAMTS in chondrocytes, preventing the degradation of articular cartilage.[140] A specific small molecule inhibitor of MMP-13 has demonstrated efficacy in attenuating OA severity in a meniscal injury-induced model.[141]

In addition to proteinase inhibitors, the transcription factor Runt domain factor-2 (Runx2) emerges as a promising target for regulating MMP-13 and ADAMTS5 in vivo. DNA sequence analyses of Mmp-13 and Adamts5 promoters have identified putative Runx2 binding sites within the promoter regions of these genes. Furthermore, Runx2 exhibits an overlapping expression pattern with MMP-13 and ADAMTS5, predominantly localized in developing cartilage and bone, suggesting that Runx2 may play a critical role as a transcription factor regulating the tissue-specific expression of Mmp13 and Adamts5 in articular chondrocytes.[142–144] Thus, modulating Runx2 expression in vivo could represent an effective therapeutic approach. During bone development, the spatiotemporal expression patterns of Runx2 are regulated by cytokines and growth factors, including TGF-β, BMP, and FGF.[145–148] Besides gene expression, Runx2 protein levels are subject to regulation through post-translational modifications, such as phosphorylation, ubiquitination, and acetylation.[149–154]

Additionally, microRNA regulation constitutes a vital mechanism influencing protein translation. MicroRNA-140 (miR-140) has been implicated in OA pathogenesis, at least in part through its regulation of ADAMTS5 mRNA expression. MiR-140 knockout mice exhibit increased susceptibility to age-related OA progression, whereas overexpression of miR-140 in chondrocytes confers protection against OA development.[155–157]

CONCLUSION

Osteoarthritis (OA) represents a multifactorial degenerative disease of the joints characterized by a progressive deterioration of articular cartilage, subchondral bone changes, and synovial inflammation. As discussed, the molecular mechanisms underlying OA are complex and involve a myriad of biochemical pathways and cellular processes. This review highlights critical insights into the role of molecular players, particularly transforming growth factor-beta (TGF-β), in the pathogenesis of OA. The multifaceted nature of OA emphasizes the importance of addressing both mechanical and biological factors in its management. The dysfunction of chondrocytes, primarily driven by an imbalance in anabolic and catabolic signals, leads to the degradation of the extracellular matrix, a hallmark of OA progression. The loss of TGF-β signaling, which typically inhibits chondrocyte hypertrophy and maintains cartilage integrity, is especially noteworthy. As this pathway is found to switch from protective to catabolic roles with aging, this has significant implications for therapeutic interventions, suggesting that a nuanced approach may be necessary for older populations. Moreover, the identification of genetic predispositions and the impact of mechanical stresses underscore the necessity for personalized treatment strategies that consider individual risk factors. Current management strategies, including pharmacological interventions and lifestyle modifications, primarily target symptom relief rather than halting disease progression. This highlights an urgent need for further research into molecular therapies that could potentially modify disease trajectory. Future research should focus on exploring the potential of emerging biologics that target specific pathways implicated in OA, including the TGF-β signaling cascade. The development of disease-modifying osteoarthritis drugs (DMOADs) could revolutionize OA management by preserving cartilage health and improving joint function, ultimately enhancing the quality of life for millions affected by this debilitating condition. As we move forward, a deeper understanding of OA's molecular pathogenesis will be crucial in developing effective and targeted therapies.

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هشاشة العظام: التحقيق في آليات التسبب الجزيئي - مقالة مراجعة

الملخص:

خلفية: تُعد هشاشة العظام (OA) أكثر اضطرابات المفاصل المزمنة شيوعًا، وخاصةً بين الأفراد الذين تتجاوز أعمارهم 65 عامًا. مع ارتفاع معدل الإصابة والتأثير الاجتماعي والاقتصادي الكبير، لا تزال تمثل تحديًا كبيرًا في مجال الرعاية الصحية لكبار السن. تتميز هشاشة العظام بالألم المزمن، التيبس، وقلة الحركة، بينما تركز خيارات العلاج الحالية بشكل رئيسي على تخفيف الأعراض بدلاً من معالجة الآليات الفسيولوجية المرضية الأساسية.

الهدف: تهدف هذه المراجعة إلى توضيح الآليات الجزيئية التي تؤدي إلى نشوء هشاشة العظام، مما يسلط الضوء على الأهداف العلاجية المحتملة للوقاية والعلاج.

الطرق: تم إجراء مراجعة شاملة للأدبيات العلمية شملت دراسات حديثة حول بيولوجيا الخلايا والجزيئات الغضروفية المفصلية، ودور عوامل النمو، الاستعدادات الجينية، والعوامل الميكانيكية في تطور هشاشة العظام.

النتائج: تكشف النتائج أن الغضروف المفصلي يخضع لتغيرات هيكلية وتركيبية كبيرة خلال تقدم هشاشة العظام. تشمل اللاعبين الجزيئيين الرئيسيين عامل النمو المحول بيتا(TGF-β) ، الذي يؤثر على سلوك الخلايا الغضروفية وتكوين المصفوفة، وعدة سيتوكينات التهابية تزيد من تدهور الغضروف. تساهم العوامل الجينية والإصابات السابقة للمفاصل أيضًا في الاستعداد للإصابة وتقدم هشاشة العظام.

الخلاصة: يوفر فهم التسبب الجزيئي لهشاشة العظام رؤى حول استراتيجيات علاجية جديدة تهدف إلى تغيير تقدم المرض. استهداف مسارات جزيئية محددة، لا سيما تلك التي تشمل TGF-β وآليات الإشارة المرتبطة به، يوفر فرصة لتطوير تدخلات فعالة للحفاظ على صحة المفاصل.

الكلمات المفتاحية: هشاشة العظام، الآليات الجزيئية، TGF-β، الخلايا الغضروفية، تدهور الغضروف، الأهداف العلاجية.