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REVIEW

Research progress and prospect of MAPK signaling pathway in knee osteoarthritis

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Abstract

The knee joint, one of the most vulnerable joints in the human body, is susceptible to degenerative changes due to factors such as aging, obesity, trauma, inflammation, and genetic predisposition. These factors contribute to primary or secondary degeneration of knee joint cartilage and bone hyperplasia. Knee osteoarthritis (KOA), a prevalent condition particularly among the elderly, significantly impacts patients' quality of life. Aberrant activation of cellular signaling pathways, namely the NF-κB, MAPK, and Wnt pathways, has been identified as a key factor in the pathogenesis of KOA. These pathways contribute to inflammation, cartilage degradation, and disruption of the anabolic–catabolic balance within articular cartilage. Understanding the precise roles of these pathways is crucial for developing targeted therapies to prevent and treat knee OA. Therefore, further exploration of the pathogenesis of knee osteoarthritis is essential to develop more effective therapeutic strategies.

Keywords Knee osteoarthritis · Research progress · Mitogen-activated protein kinase (MAPK) signaling pathway · Inflammatory response

Introduction

Osteoarthritis of the knee (KOA) is the most prevalent chronic degenerative disease in the world today. Its prevalence is increasing year on year. By 2050, the global number of individuals affected by knee osteoarthritis is projected to reach 642 million [1]. In the development of knee osteoarthritis, trauma, obesity, aging, stress and genetics are important causes of its development, as shown in Fig. 1. Cartilage function and autologous repair rely heavily on metabolic regulation, and when this regulation is disrupted, abnormal extracellular matrix (ECM) synthesis occurs [2] Among the signaling molecules that can modulate many biological reactions, the extracellular matrix (ECM), one of the components of the ECM, also maintains the dynamic integrity of tissues, which is why most chronic diseases are caused by dysregulation of the ECM. External factors such as inflammation, injury, and infection can alter the chemical composition and mechanical properties of the ECM, initiating a cascade of events that impact immune processes [3]. Knee osteoarthritis has been further categorized into four subtypes: cartilage breakdown-based, bone reconstruction-based, inflammation-based and pain-based, based on the predominant pathophysiology [4]. The pathogenesis of knee osteoarthritis is multifaceted, the primary cause being destabilization of the intra-articular environment and the destruction of articular cartilage involving a complex interplay of cytokines, growth factors and signaling pathways [5].

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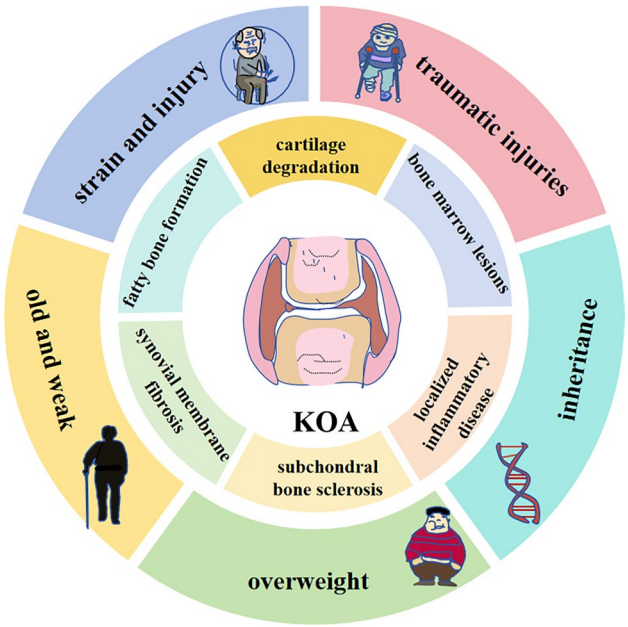

Fig. 1 Knee osteoarthritis pathogenesis factors influence diagram

The mitogen-activated protein kinase (MAPK) cascade, a highly conserved signaling pathway, is crucial for mediating cellular responses to diverse stimuli [6]. A three-tiered system of protein kinases is responsible for regulating gene expression and controlling cellular behavior. This system functions by relaying signals from the cell surface to the nucleus. Aberrant MAPK signaling has been implicated in a range of diseases, highlighting its importance in maintaining cellular homeostasis. There are four branches of this signaling pathway, namely ERK, p38, JNK, and ERK5, as shown in Fig. 2 (By FigDraw.).The MAPK signaling pathway regulates biological processes such as cell proliferation, cell death, differentiation and inflammatory responses in multiple cells and tissues [7]. The MAPK signaling pathway is emerging as a key player in the pathogenesis of knee OA. Abnormal activation of this pathway contributes to the inflammatory response, cartilage degradation, and chondrocyte dysfunction. Further investigation into the discrete roles of specific MAPK signaling pathways, such as extracellular signal-regulated kinase (ERK) and c-Jun NH2-terminal kinase (JNK), has the potential to offer valuable insights for advancement of targeted therapeutic interventions for KOA. Studies have indicated that the MAPK signaling pathway in KOA regulates articular chondrocyte metabolism and function of articular chondrocytes, and the MAPK signaling pathway may contribute to degenerative changes of articular cartilage and trigger the inflammatory response [8]. Specifically, the c-Jun N-terminal kinase (JNK) and p38/MAPK signaling pathways can be activated in KOA, which in turn regulates the apoptosis (programmed cell death) of joint chondrocytes (cartilage cells) and the production of inflammatory factors. This, in turn, exacerbates cartilage damage [9]. KOA can arise as a result of articular chondrocyte death and degradation brought on by ERK hyperactivation. Conversely, transient activation of the ERK pathway can in turn lead to transient proliferation of chondrocytes, potentially resulting in chondroplasia and ultimately joint dysfunction [10, 11]. An important role for the MAPK signaling pathway in the pathophysiology of KOA is its contribution to

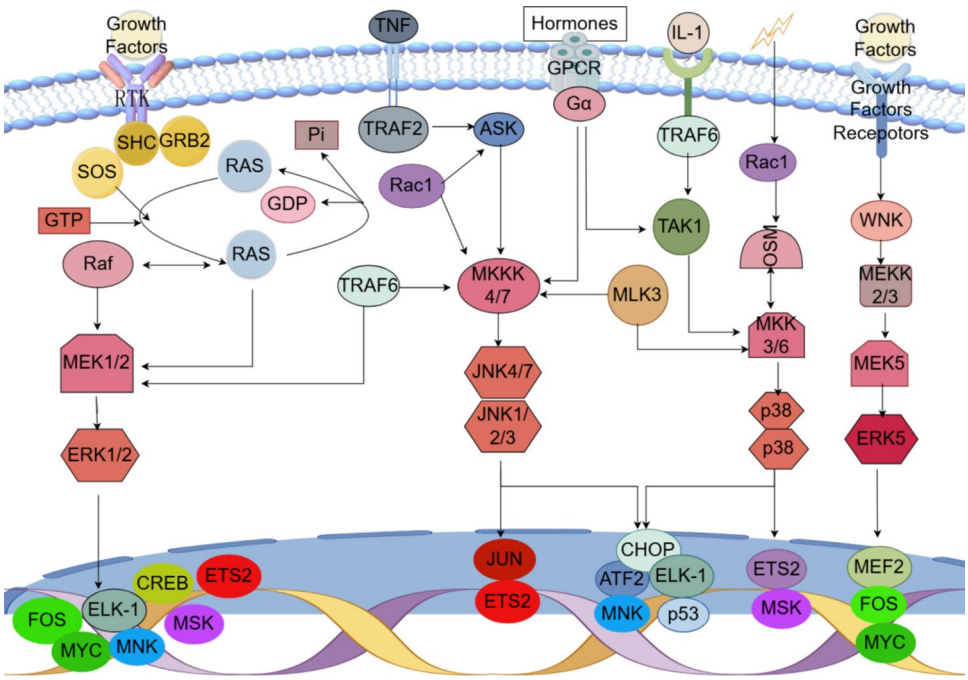

Fig. 2 An illustration of the branching of the MAPK signaling pathway

chondrocyte death, inflammation and deterioration of cartilage. To further understand the intricate processes behind KOA and identify possible therapeutic targets for the illness's prevention and therapy, more research is necessary.

Relevant active factors, enzymes and drug carriers capable of influencing the expression of the MAPK signaling pathway in KOA

Insulin-like growth factor-1 (IGF-1)

Strong growth factors such as insulin-like growth factor-1 have been shown to promote chondrocyte cell proliferation and matrix production, two essential processes for cartilage growth and repair. The expression correlates with the successful regeneration cartilage. IGF-1 activates the MAPK signaling pathway, promoting cartilage repair while mitigating inflammation, highlighting its therapeutic potential in cartilage regeneration [12]. Both MKP-1 and IGF-1 are significant regulators in the process of bone formation. The role of MKP-1 is generally regarded as inhibit bone formation, whereas that of IGF-1 promotes bone formation. MKP-1 inhibits IGF-1 signaling by dephosphorylating and inhibiting key proteins in the MAPK pathway. This will reduce the IGF-1 ability to stimulate bone growth. Jingwu Zang et al. investigated the effects of varying doses of IGF-1 on the cartilaginous layer and subchondral bone (SB) during the repair of full-thickness articular cartilage defects [13]. IGF-1 displays a dose-dependent effect on musculoskeletal regeneration. IGF-1's specific activation of the ERK signaling pathway promotes osteoblast differentiation. Meanwhile, it is found that high-dose IGF-1 favored cartilage formation and integration, while low doses were more effective in stimulating SB formation [14]. These results demonstrate the possibility of specific therapeutic uses of IGF-1 in the regeneration of bone and cartilage. Moreover, the effects of IGF-1 on bone formation were enhanced by suppression of mitogen-activated protein kinase phosphatase-1, a negative regulator of the MAPK family. According to these results, MKP-1 could be a useful target for treating knee osteoarthritis, which could improve the effectiveness of IGF-1-based treatments.

MMPs and ADAMTS

Matrix metalloproteinases (MMPs) and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) are proteolytic enzymes that have a crucial function in the pathogenesis of KOA. The MMP family, encompassing MMP-1, MMP-9 and MMP-13, among others, are primary contributors to the degradation of the cartilage matrix [15]. Elevated MMP-1 expression has been observed in KOA chondrocytes, while increased MMP-9 secretion has been shown to accelerate the arthritic response in KOA and promote cartilage degeneration [16]. Conversely, MMP-13 interacts with MMP-1 degradation and also triggers chondrocyte death, thereby influencing the degenerative changes within articular cartilage. Experimental studies have demonstrated that subchondral osteoblasts in OA affect the expression of ADAMTS-4, ADAMTS5, MMP-3, MMP-9 and MMP-13 in chondrocytes, and regulate the mitogen-activated protein kinase (MAPK) signaling pathway [17].

Extracellular vesicles

Cells produce spherical objects called extracellular vesicles, which are membrane-bound structures. They serve as carriers of bioactive molecules, including nucleic acids and proteins. These vesicles serve as intercellular messengers, facilitating the transfer of these molecules between cells. Extracellular vesicles hold promise as drug delivery vehicles due to their inherent biocompatibility and ability to target specific cells. Extracellular vesicle miRNAs are involved in intercellular communication and have been implicated as a contributing factor in the pathogenesis of knee osteoarthritis [18]. Notably, KEGG pathway enrichment analysis also revealed that the MAPK signaling route, cell adhesion plaques and the FoxO signaling pathway—three pathways essential to cartilage function—were considerably overrepresented in differentially expressed microRNA target genes [19]. These findings provide novel insights into the mechanisms underlying cartilage damage and KOA pathogenesis, suggesting potential avenues for the development of improved diagnostic and therapeutic strategies for this debilitating condition [20].

Vascular endothelial growth factor

Vascular endothelial growth factor, a key regulator of blood vessel permeability, promotes cell migration, proliferation, and survival. VEGF's influence on blood vessel formation and growth is mediated through the VEGF signaling pathway, which includes the Ras/MAPK cascade [21]. This cascade controls cell division and gene expression. Studies have demonstrated that the degeneration of articular cartilage is a time-dependent process, with the expression of the VEGF-A/VEGF2 signaling pathway strongly correlating with the severity of knee osteoarthritis [22]. VEGF triggers the activation of p38-MAPK, contributing to chronic inflammation. This inflammatory response subsequently leads to a reorganization of the actin cytoskeleton and promotes endothelial cell migration [23].

It's so important to understand how these different branches (including ERK, p38, JNK and ERK5) work in body, especially when it comes to KOA. Once we know more about how they behave, we can start to develop new ways to treat the condition

The mitogen-activated protein kinase signaling pathway encompasses discrete branches, each of fulfills a distinctive role in the etiology of knee osteoarthritis. A comprehensive understanding of the expression patterns and mechanisms of action of the aforementioned pathways, including those of ERK, p38, JNK, and ERK5, is essential for the development of novel therapeutic strategies in in the treatment of KOA. Within KOA lesions: ① activation of the MAPK/ERK signaling pathway has been implicated in both cartilage repair mechanisms and the development of cartilage overgrowth and osteochondrosis formation [24, 25]. Investigating the activation of Runx2 transcription factor, a key regulator of osteoblast differentiation, Kanno T et al. [26] demonstrated that mechanical stress induces Runx2 activation through MAPK pathway activation and Ras/raf-dependent ERK1/2 activation, thereby promoting osteoblast differentiation. ②The MAPK/p38 signaling pathway has been implicated in cartilage degeneration, characterized by the release of inflammatory mediators [27, 28], Ma Qing hou et al. showed experimentally evidence that activation of the p38-MAPK signaling pathway can cause mitochondrial dysfunction leading to oxidative stress and apoptosis in human chondrocytes and cartilage degeneration [29]. Furthermore, activation of the MAPK/JNK signaling pathway is associated with both cartilage degeneration and extracellular matrix degradation [30]. In an in vitro model of osteoarthritis, Gremlin-1 has been shown to induce cellular inflammation and ECM degradation in the human chondrocyte line CHON-001 with IL-1β by activating the MAPK signaling pathway [31]; ④The MAPK/ERK5 signaling pathway plays a critical role in chondrocyte proliferation and differentiation. Studies by Wang X et al. have demonstrated that fluid shifting stress, under specific conditions, maintains osteoblast skeletal structure and function and promotes osteoblast proliferation through activation of the ERK5 signaling pathway, a pathway intimately associated with the development of knee osteoarthritis [32, 33]. As osteoarthritis worsens, IL-1β increases Wnt5a expression, which via the JNK signaling pathway then raises matrix metalloproteinase production [34]. Zhao Chengwu et al. [35] investigated the expression of CAP1, lipotropic resistance factor, as well as CCL3, CCL4, MMP-13 and ADAMTS-4 in chondrocytes from KOA patients. According to their research, these elements can activate the p38-MAPK and NF-κB signaling pathways, which in turn can increase the expression of matrix-degrading enzymes and pro-inflammatory cytokines.

Exploring the regulatory mechanisms of the MAPK signaling pathway on articular chondrocyte function and inflammatory response in KOA

MAPK signaling pathway and articular chondrocytes in KOA

Articular chondrocytes, the primary cell type of articular cartilage, are responsible for the dynamic balance of cartilage matrix breakdown and synthesis, essential for maintaining normal cartilage structure and function [36]. The mitogen-activated protein kinase signaling pathway exerts a multifaceted influence on chondrocyte biology, impacting both anabolic and catabolic processes. Specifically, MAPK signaling pathway can: (1) activate transcription factors, such as AP-1 [37] and CREB [38] to encourage the production of cartilage matrix proteins, such as proteoglycans and type II collagen, helping to preserve the structure and function of cartilage; (2) activate degradative enzymes, such as matrix metalloproteinase and a disintegrin and metalloproteinase with thrombospondin motifs, leading to cartilage matrix degradation and accelerating cartilage degradation [39]; and (3) induce chondrocyte apoptosis, further contributing to accelerate cartilage degradation. The activation of receptor activator of nuclear factor κB ligand (RANKL) triggers the phosphorylation of ERK, p38, and JNK, signaling pathways implicated in osteoclast differentiation [40]. Studies have demonstrated that RANKL [41] significantly enhances the phosphorylation levels of ERK, p38, and JNK during the differentiation of macrophages into OCs. In the study of Jiang Ting et al., inhibiting ERK activity using PD0325901 in RANKL-stimulated bone marrow mononuclear cells was shown to suppress the RANKL-induced expression of osteoblast marker genes, such as c-fos and NFATC1 [42]. This highlights the critical role of ERK signaling in osteoclast genesis. Cartilage degeneration is a heterogeneous process, encompassing the death of chondrocyte, the degradation of the cartilage matrix, and a subsequent loss of cartilage function [43]. Fibroblast growth factor 2 is a pleiotropic growth factor that exerts a complex influence on this degenerative process. While FGF-2 promotes cartilage and bone tissue repair by acting as a mitogen and morphogen for chondrocytes, its role in cartilage degeneration is multifaceted. In healthy cartilage, basic FGF, a key regulator of chondrocyte differentiation and cartilage-specific gene expression, induces the expression of Sox9 [44]. This suggests that FGF signaling plays a crucial role in maintaining

cartilage homeostasis. However, the MKK/MEK1/2 inhibitor U0126 blocks Sox9 induction, implying that the ERK pathway is vital for chondrocyte phenotype expression [45]. Furthermore, the ERK and p38 signaling pathways must both be activated in order to block FGF-induced chondrocyte development [46, 47]. This finding suggests that ERK and p38 may be involved in both chondrogenesis and the maintenance of cartilage homeostasis.

MAPK/ERK signaling plays a crucial role in bone formation. It has been shown that phosphorylation of MAPK/ERK improves angiogenesis [48], a process essential for bone growth. Additionally, autophagy, a cellular process involved in the degradation of cellular components, enhances the secretion of vascular endothelial growth factor in mesenchymal stem cells, contributing further to angiogenesis. Autophagy serves as a signaling mediator in the response to fibroblast growth factor signaling [49]. This process is crucial for regulating various cellular functions, including cell growth, differentiation, and survival. In the context of bone formation, autophagy plays a significant role in modulating the activity of FGFs, ultimately influencing bone development. Via the MAPK/JNK pathway, fibroblast growth factor 18 triggers the BECN1-mediated endochondral bone formation process [50]. BECN1, an essential autophagy-related protein, is a key component of this pathway. FGF18 stimulation has been demonstrated to trigger the activation of MAPK/JNK, which in turn leads to the phosphorylation of BECN1. This phosphorylation event promotes BECN1-mediated autophagy, which is essential for the normal development and function of chondrocytes, the cells responsible for forming cartilage in endochondral bone formation. The results of studies on c-MpI knockout mice have indicated an increased bone mass at six months of age [51], while the precise mechanism of this observation remains under investigation, and it suggests a potential role for c-MpI in regulating bone formation. And p38-MAPK, a pivotal member of the MAPK family, regulates osteoblast differentiation. Osteoblasts are responsible for bone formation, and their differentiation process is tightly controlled by signaling pathways such as p38-MAPK, and activation of this pathway promotes osteoblast differentiation, thereby contributing to the overall process of bone development [52]. This finding serves to further highlights the intricate relationship between the various signaling pathways, including those involving MAPK signaling, and their influence on bone development. GPER1, a novel estrogen receptor, has been shown to play a role in bone metabolism. Upon activation, GPER1 promotes intracellular calcium mobilization, followed by rapid phosphorylation of ERK1/2, a key component of the MAPK/ERK pathway. This phosphorylation event leads to increased osteoblast proliferation, indicating a potential role for GPER1 in regulating bone formation through MAPK signaling [53].

MAPK signaling pathway and inflammatory response in KOA

The mitogen-activated protein kinase signaling pathway plays a crucial role in the pathogenesis of osteoarthritis. Tumor necrosis factor alpha, interleukin-6 and interleukin-1 beta are a few of the inflammatory factors that are produced when the MAPK pathway is activated [54, 55]. This inflammatory cascade, in turn, further activates the MAPK pathway, perpetuating a cycle that promotes cartilage matrix degradation and chondrocyte apoptosis resulting in cartilage damage. Moreover, aberrant chondrocyte proliferation induced by the MAPK pathway disrupts cartilage structure and function.

KOA is a particular kind of OA that affects the knee. It is defined by pathological circumstances where tissue proteases break down the articular cartilage's extracellular matrix [56]. While inflammation typically involves the activation of intracellular signaling pathways, in the context of OA, these pathways are often blocked, leading to the inhibition of protein kinases and the suppression of inflammatory mediator and protease production [57]. The important inflammatory response gene cyclooxygenase-2 is expressed more often in knee cartilage during osteoarthritis [58]. Prostaglandin E2 has been shown to negatively regulate inflammatory gene expression and inhibit cell proliferation [59]. Interleukin-1, an extracellular catabolic agent in cartilage, contributes to the breakdown of the extracellular matrix by inhibiting proteoglycan and collagen synthesis [60]. Elevated expression of MMP-13 in cartilage is a hallmark of inflammation [61]. Inflammatory factors, such as interleukin-1 and tumor necrosis factor-α, can alter the anabolic behavior of chondrocytes. The mitogen-activated protein kinase pathway plays a multifaceted role in regulating inflammatory processes. While it can inhibit JNK to mitigate ischemia-related cell death, the ERK and p38 pathways are generally considered pro-apoptotic, potentially contributing to cell death [62]. In a rabbit model of knee osteoarthritis induced by anterior cruciate ligament transection, PD198306 administration has demonstrated efficacy in reducing cartilage size and histological damage, and this effect is accompanied by a decrease in inflammatory factor levels within the synovial membrane and a reduction in immunostaining for active ERK and MMP-1 [63]. Reactive oxygen species are known to influence inflammation some activation, and their elevated levels during knee osteoarthritis pathogenesis contribute to apoptosis [64]. Furthermore, ROS promote the secretion of interleukin-1beta and interleukin-18, exacerbating chondrocyte damage and cartilage matrix degradation. The MAPK signaling pathway holds significant promise for the treatment of KOA. Extensive research has illuminated the intricate role of the MAPK pathway in the complex pathogenesis and physiological processes of KOA

[65]. Further investigation into the specific mechanisms by which this pathway contributes to KOA development and progression is essential. The identification of novel drug targets within the MAPK pathway, along with the development of targeted therapies, offers the potential for effective KOA treatment strategies [65].

Discussion

The MAPK signaling pathway has great potential for the treatment of KOA, and more research should be done on the role of the MAPK signaling pathway in the pathology and physiology of KOA and the development of new drugs, etc. The MAPK signaling pathway is likely to be an effective treatment for KOA. As a rational regulation of the MAPK signaling pathway and its related pathways, we hope to better understand the mechanism of the MAPK signaling pathway in KOA, provide a scientific basis for further research and development of related therapeutic approaches, and provide clinicians with more effective interventions to improve the quality of life of KOA patients.

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Author contribution Specific author contributions: Q.F. and M.Z. wrote and typeset the manuscript; X. Z. and T.C. performed literature corrections and additions; Z.K. and Q.Z. plot Figs. 1 and 2. All authors reviewed the manuscript, finally drafting of the manuscript and study supervision.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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