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ERK Pathway in Osteoarthritis: A Review of Pharmacological and Natural Interventions

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Abstract

Osteoarthritis (OA) is a chronic degenerative joint disease that leads to disability and affects quality of life. Several biochemical signaling axes are related to the OA progression, such as the extracellular regulated kinase (ERK) signal transduction pathway. Because ERK is a versatile and multi-functional transcription factor associated with many biological programs, a comprehensive understanding of the function or modulation of ERK in the OA pathology will aid in the development of targeted treatment strategies to protect the cartilage from OA damage and decrease the risk of side effects. In this review, we discuss the roles of ERK in OA chondrocytes and related signaling cascades, including recent findings, to better understand pathological cartilage remodeling and provide potential therapeutic targets that can interfere with ERK signaling for OA treatment.

Keywords

Osteoarthritis, ERK Signaling Pathway, Chondrocytes, Natural Products, Cartilage Degradation

1. Introduction

Osteoarthritis (OA), a degenerative disorder that impacts synovium, articular cartilage, and subchondral bone, has become the primary factor that causes disability among older people throughout the world [1] [2]. Therefore, the prevalence of

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OA is continuously increasing because of the rise in the geriatric population. The abnormal metabolism of chondrocytes, synovium, subchondral bone, and extracellular matrix (ECM) in joint tissue results in the degradation of cartilage, subchondral sclerosis, synovial inflammation, osteophyte formation, and subchondral cysts [2]. The significant clinical symptoms of OA include stiffness, pain, tenderness, swelling, and effusion [3] [4]. Currently, the main approved treatment for OA is supportive to alleviate the manifestations, including glucosamine, corticosteroid, or hyaluronic acid (HA) injections, and non-steroidal anti-inflammatory drugs (NSAIDs) [5] [6]. Indeed, no licensed disease-modifying drugs are available to prevent the progression of OA. Unfortunately, a joint replacement surgery will be recommended in severe cases of OA [7]. Thus, we urgently need to identify more effective targets and develop new approaches to treat and prevent OA.

Chondrocytes maintain cartilage homeostasis by synthesizing ECM, thus preserving the structural and functional integrity of the cartilage. Thus, the gradual loss of chondrocytes is supposed to be the main cause of OA [8]. Chondrocytes are involved in a terminal differentiation process to synthesize cartilage through several signaling cascades, including phosphoinositide 3-kinase (PI3K)/AKT, Wnt/β-catenin, nuclear factor-kappaB (NF-κB), and mitogen-activated protein kinases (MAPKs; p38, ERK, and c-Jun N-terminal kinase (JNK) [9] [10]. Disturbance in the signaling pathways causes an alteration in chondrocyte behavior, they converse to catabolic cells that secrete matrix-degrading enzymes, such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs). As a result, alteration in chondrocyte behavior leads to cartilage degeneration and the replacement of cartilage by bone [11] [12].

The ERK signaling pathway is a master protein kinase that phosphorylates various downstream substrates involved in a multitude of cellular functions, including cell proliferation, differentiation, survival, death, and motility [13] [14]. Furthermore, ERK is related to the immune response, embryonic morphogenesis, and skeletal development [15]-[17]. Most importantly, aberrant activation of the ERK pathway has been shown to be an essential feature common to many types of pathological conditions, such as cancer, neurological, inflammatory, cardiac hypertrophy, and autoimmune disease [13] [18] [19]. In this study, we try to analyze the relation of the ERK signaling cascade in the development and progression of OA, and demonstrate the effort to target this cascade to treat and prevent the disease condition.

2. Basic Mechanism of the ERK Pathway

ERK is a central component in the MAPK signaling pathway, also called the 42-/44-kDa mitogen-activated protein kinase pathway [20]. The members of the ERK superfamily have been shown to consist of ERK 1, 2, 3, 5, and 6 [21]. However, ERK1/2 plays the most important role among these members, which are encoded by two splice variants of the same gene and share approximately 80% similarity [21].

ERK is classically initiated at the cell membrane and activated by a variety of stimulating factors such as growth factors, several cytokines, and microbial products

[21]. Key molecules in the ERK signaling pathway mainly include the small G protein Ras and downstream Raf kinase, MEK1/2, and ERK. After stimulation of the appropriate (cognate) receptor, a Src homology 2 domain-containing protein (Shc) recruits the Grb2 protein and the son of sevenless (SOS) homolog protein, resulting in the loading of membrane-bound Ras with GTP [22]. GTP then recruits Raf to the membrane, where it becomes activated, likely via a Src-family tyrosine (Y) kinase [23]. Raf is responsible for serine/threonine (S/T) phosphorylation of mitogen-activated protein kinase kinase-1/2 (MEK1/2). MEK1/2 phosphorylates ERK at specific T and Y residues [24]. Activated ERK can translocate to the nucleus and directly phosphorylate additional transcription factors, such as Elk-1, CREB, Fos and globin transcription factor 1 (Gata-1) and others [25] [26], that bind promoters of many genes, including growth factor and cytokine genes that are important in promoting growth, proliferation, survival, migration and differentiation, and preventing apoptosis of multiple cell types [27] [28]. **Figure 1** represents the basic mechanism of the ERK pathway.

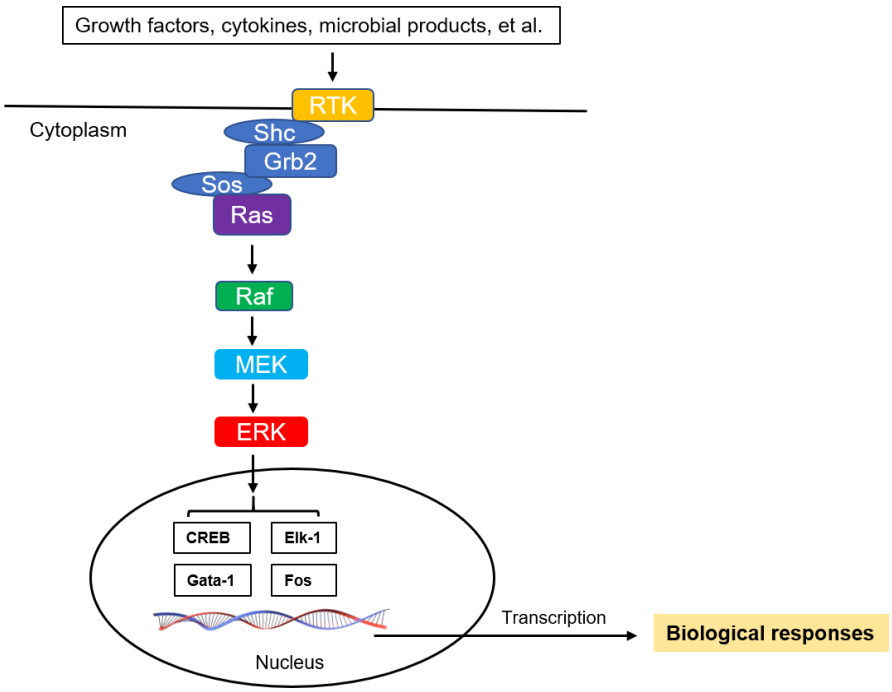

Figure 1. Basic mechanism of the ERK signaling cascade. ERK is activated by a variety of growth factors, several cytokines, and microbial products [21]. Key molecules in the ERK signaling pathway mainly include Shc, SOS, the small G proteins Ras and downstream Raf kinase, MEK1/2, and ERK [24]. Activated ERK can translocate to the nucleus and directly phosphorylate additional transcription factors, such as Elk-1, CREB, Fos, and Gata-1, and others [25] [26].

3. ERK Pathway in Osteoarthritis Progression

3.1. Pathological Hyperactivation of ERK and Core Matrix Degradation

The underlying mechanisms that stimulate the alteration of chondrocytes and

subsequent cartilage breakdown in osteoarthritis (OA) remain fully elucidated; however, these cellular alterations are heavily supposed to contribute to the progressive destruction of joint tissue in OA [29]. The extracellular regulated kinase (ERK) cascade represents one of the most complex signaling axes within the joint microenvironment, and accumulated evidence has shown that the pathological activation of this pathway directly relates to the pathogenesis and progression of OA. According to previous studies, a much higher phosphorylation (activation) level of ERK is consistently captured in tissue exhibiting a greater degree of OA compared with normal tissue, thereby indicating that it plays an important role in the destruction of articular cartilage [30].

Mechanistically, the abnormal phosphorylation of ERK stimulates activator protein 1 (AP-1) activation. This downstream nuclear event results in reduced chondrocyte proliferation, diminished type II collagen synthesis, and suppressed proteoglycan production, while simultaneously driving the increased expression of cartilage-degrading enzymes, most notably matrix metalloproteinase (MMP)-13. A growing body of reports has indicated that such MMP-13 overproduction by chondrocytes holds a central and indispensable role in the degeneration of cartilage matrix [29]. Characterizing the intermediates of this cascade, Otero *et al.* [30] speculated that E74-like factor 3 (ELF3) acts as a critical MEK/ERK downstream effector, which stimulates abnormal MMP13 expression and activity in chondrocytes and other joint cell types when they respond to environmental stress and inflammatory stimuli. Therefore, the precise regulation of the MEK/ERK/ELF3 signaling pathway may be one of the key contributing factors governing the development and phenotypic progression of human OA.

3.2. Cell-Type Specific Dynamics of ERK in the Joint Microenvironment

While cartilage erosion is the hallmark of OA, the joint functions as an integrated organ; consequently, the hyperactivation of ERK signaling exerts distinct, cell-type-specific effects across different cellular compartments within the joint microenvironment, shifting the entire joint toward a catabolic state.

Articular Chondrocytes: Within the cartilage layer, altered ERK activity disrupts homeostatic maintenance. Takagi *et al.* reported that the upregulated activation of ERK, p38, and STAT3 cascades can induce IL-6 and RANKL expressions, which are directly related to cartilage destruction-related processes, including phenotypic dedifferentiation and chronic inflammatory responses in OA chondrocytes [31]. This sustained ERK activation shifts chondrocytes from an anabolic phenotype to a hypertrophic and senescent state, accelerating cartilage matrix collapse.

Synovial Fibroblasts: In fibroblast-like synoviocytes (FLSs), abnormal ERK activation serves as a major driver of synovitis. Responding to mechanical overload and alarmins, hyperphosphorylated ERK in FLSs accelerates the transcription of pro-inflammatory cytokines and chemokines, establishing a deleterious

feed-forward inflammatory loop that aggravates joint pain and swelling.

Subchondral Bone Cells: Beneath the tidemark, ERK signaling in subchondral osteoblasts and osteoclasts modulates aberrant bone remodeling. Pathological ERK activation in osteoblasts enhances abnormal osteogenesis, contributing to the subchondral bone sclerosis and marginal osteophyte formation that characterize advanced OA stages.

3.3. Crosstalk with Inflammatory Cytokines and Metabolic Mediators

The intracellular ERK cascade does not operate in isolation; rather, it is embedded in a complex crosstalk network involving various inflammatory cytokines, adipokines, and stress-induced kinases that synergistically accelerate cartilage breakdown.

Prostaglandin E2 (PGE2) represents a primary inflammatory mediator downstream of this network. Masuko-Hongo *et al.* [32] reported that activating ERK and p38 signaling cascades significantly promotes the formation of PGE2, which possesses several functions involved in cartilage breakdown in OA patients, including the modulation of proteoglycan and collagen synthesis and the stimulation of chondrocyte apoptosis. Furthermore, metabolic factors heavily intersect with this pathway; Hui *et al.* [33] reported that the adipokine leptin plays a critical role in the inflammatory and degenerative processes in cartilage degradation via the upregulation of proteolytic enzymes with a concomitant activation of STAT1, STAT3, STAT5, MAPK (JNK, ERK, p38), AKT, and NF-κB signaling pathways.

This catabolic cascade is prominently fueled by upstream alarming cytokines. Dai *et al.* reported that IL-1β and TNF-α induce the levels of MMP1, MMP3, MMP13, ADAMTS4, and ADAMTS5 transcription, playing important roles in cartilage degradation in OA [34]. Intriguingly, these destructive effects are inhibited by the depletion of Brd4 and Brd3 through suppressing the downstream NF-κB, JNK, and ERK signaling pathways [34]. Furthermore, cellular stress kinases directly feed into this axis; Ma *et al.* [35] reported that the double-stranded (ds) RNA-dependent protein kinase (PKR) leads to OA pathogenesis by regulating critical molecular events, including oxidative stress (characterized by elevated NOX expression and ROS formation), inflammatory responses, and matrix degradation, through inducing the ERK/NF-κB signaling axis. Additionally, epigenetic modulators tightly control this cascade. Wang *et al.* suggested that histone deacetylase (HDAC) 4 and HDAC 8 may serve as key upstream mediators of JNK and ERK in regulating the IL-1β-induced cartilage catabolic changes and degradation [9].

4. Targeting the ERK Pathway in Osteoarthritis Treatment

Osteoarthritis (OA) is a highly prevalent degenerative joint disorder characterized by chronic inflammation and progressive cartilage degradation, posing a substantial threat to healthy living and patient quality of life. Current clinical therapies

targeting OA predominantly focus on symptom relief, whereas disease-modifying osteoarthritis drugs (DMOADs) that effectively halt OA progression remain to be fully explored. Given its pivotal role in catabolic and inflammatory networks, targeting the ERK signaling pathway represents a promising therapeutic avenue for the prevention and treatment of OA. **Table 1** summarizes the major treatment strategies for OA and the corresponding phenotypic consequences achieved by targeting the ERK pathway.

Table 1. The main therapeutic strategies of OA and the consequences of targeting the ERK cascade.

Therapeutic Agent	Experimental Model	Effects	References
Isorhapontigenin (ISO)	Rat Chondrocytes	Suppressed the IL-1β-induced inflammation and cartilage matrix damage	[36]
Kinsenoside (Kin)	Chondrocytes	Attenuated IL-1β-induced chondrocyte damage	[37]
Anthocyanins and Metabolites	Chondrocytes	Inhibited IL-1β-induced matrix metalloproteinases expression	[38]
Emodin	Rat Chondrocytes	Induced chondrocytes proliferation and downregulated the expression of several inflammatory mediators	[39]
Kaempferol	Rat Chondrocytes	Inhibited the IL-1β-induced expression of inflammatory mediator proteins such as COX2 and the common matrix-degrading enzymes MMP-1, MMP-3, and MMP-13	[40]
Schisandrin B	Rat Chondrocytes; Rat	Decreased IL-1β-induced upregulation of MMP-3, MMP-13, IL-6, and iNOS, and increased IL-1β-induced downregulation of collagen II and aggrecan	[41]
Echinocystic Acid (EA)	Chondrocytes	Inhibited IL-1β-stimulated the production of MMP-13, NO, and PGE2, as well as the expression of iNOS and COX-2	[42]
Gentiopicroside	Rat Chondrocytes	Inhibited IL-1β-induced inflammation response and increased Collagen type II expression	[43]
Hydrogen Sulfde (H2S)	Chondrocytes	Reversed the effect of IL-1β on the MMP-13, PGE2, and NO production and on the gene expression of COX-2, MMP-13, and iNOS	[44]
Nicotine	Chondrocytes	Inhibited MIA- or IL1β-induced chondrocyte activation via the α7 nicotinic acetylcholine receptor (α7-nAChR)	[45]
ERK Inhibitor U0126	Chondrocytes	Abrogated lactoferrin (LF) activation of BMP7 gene expression	[46]
Melatonin	Rabbit OA Model	Induced cytoprotection and anti-inflammatory effect against H_2O_2-stimulated the expression of cytotoxicity, iNOS, and COX-2	[47]
Inhibition of ERK with PD98059	Rabbit Chondrocytes	Suppressed SIRT2-induced dedifferentiation and COX-2 expression	[48]
Transduction of Lysyl Oxidase Like-2 (LOXL2)	OA Chondrocytes	Inhibited chondrocyte apoptosis and increased the mRNA levels of chondroitin sulfate proteoglycan (CSPG4), aggrecan (ACAN), sex-determining region Y-box containing gene 9 (SOX9), and COL2A1, but reduced the levels of MMP-1, MMP-3, and MMP-13	[49]

Continued

Physiological Concentration of Soluble Uric Acid (sUA)	Chondrocytes	Showed anti-inflammatory and chondro-protective effect	[50]
ERK Inhibition	Chondrocytes	Exert therapeutic effect against the harmful effects of macrophage inhibition factor (MIF)-CD74 signal in human degenerated cartilage endplate (CEP) degeneration	[51]
Glycoprotein 130 (gp130)	Chondrocytes; Rat Partial Meniscectomy Model	Reduced apoptosis and hypertrophic responses, and the breakdown of cartilage matrix in regenerated cartilage	[52]
The Inhibitor of Angiopoietin-Like Protein 2 (aNgPtl2)	Chondrocytes	Downregulated the expression of the inflammation-related factor gene	[53]
IL-37	Chondrocytes	Suppressed the expression of pro-inflammatory factors via IL-1R8	[54]
Cilengitide	Chondrocytes	Inhibited the stimulation of excessive mechanically induced inflammatory reaction by upregulating the expression of IL-1β, TNF-α, MMP-3, and MMP-13	[55]
Semaphorin 3A (Sema3A)	Chondrocytes	Inhibited the gene expression of inflammatory cytokines upregulated by CTS	[56]
Focal Adhesion Kinase (FAK)	Chondrocytes	Suppressed inflammation-related factors such as COX-2, IL-1β, and TNF-α in chondrocytes under CTS	[57]
miR-125b mimic	Chondrocytes	Inhibited several pro-inflammatory cytokines and chemokines and growth factors secretion, such as IL-6, IL-8, INF-γ, IGFBP-1, and PGDF-BB	[58]
Mesenchymal Stem Cell Derived Exosomes (MSC-Exos)	Chondrocytes	Promoted the viability of chondrocytes	[59]

4.1. Plant-Derived Natural Products and Phytochemicals

Due to their prominent ERK-targeting efficacy, potent anti-inflammatory potential, and low adverse reaction profiles, natural plant extracts and phytochemicals have been widely explored as candidate therapeutic agents in OA management.

Ma *et al.* [36] reported that isorhapontigenin (ISO), a natural stilbene derivative, suppresses interleukin-1β (IL-1β)-induced elevation of nitric oxide (NO), inducible nitric oxide synthase (iNOS), prostaglandin E2 (PGE2), cyclooxygenase-2 (COX2), matrix metalloproteinases (MMPs), and ADAMTS5 in rat chondrocytes. Crucially, ISO mitigates IL-1β-induced inflammation and cartilage matrix damage by suppressing the activation of ERK and p38 signaling pathways. Similarly, Zhou *et al.* [37] investigated the chondroprotective effects of kinsenoside (Kin) to attenuate OA progression, demonstrating that Kin inhibits the core MAPK signaling molecules p-JNK, p-ERK, and p-P38, thereby alleviating IL-1β-induced chondrocyte damage. Wongwichai *et al.* [38] showed that anthocyanins and their metabolites extracted from purple rice can inhibit IL-1β-induced MMP expression by significantly blocking IκBα degradation, NF-κB/p65 phosphorylation, and

ERK signaling axis activation. Emodin, an anthraquinone isolated from Radix et Rhizoma Rhei, has long been used in traditional medicine; Liu *et al.* [39] evaluated its effects on inflammatory mediators in rat chondrocytes, revealing that emodin stimulates chondrocyte proliferation by suppressing the concurrent activation of ERK and Wnt/β-catenin signaling while downregulating downstream inflammatory targets. Furthermore, Huang *et al.* [40] revealed that Kaempferol significantly dampens the IL-1β-induced expression of inflammatory mediators (such as COX2) and common matrix-degrading enzymes (MMP-1, MMP-3, and MMP-13) via the pharmacological inhibition of mitogen-activated protein kinase-associated ERK and P38 pathways, suggesting its utility as a novel therapeutic agent. Investigating Schisandra chinensis, Ran *et al.* [41] demonstrated that its primary active component, Schisandrin B, decreases the IL-1β-induced upregulation of MMP-3, MMP-13, IL-6, and iNOS, while simultaneously rescuing the expression of Collagen II and Aggrecan. These protective effects were mediated by a significant decrease in the phosphorylation levels of p38, ERK, JNK, and NF-κB/p65, along with the suppression of NF-κB/p65 nuclear translocation.

Beyond these compounds, echinocystic acid (EA), a pentacyclic triterpene extracted from the fruits of Gleditsia sinensis Lam, exerts versatile anti-inflammatory and antioxidant actions. Ma *et al.* [42] demonstrated that EA successfully inhibits the IL-1β-stimulated production of MMP-13, NO, and PGE2, as well as the protein expression of iNOS and COX-2 in chondrocytes, via the dual inactivation of NF-κB and MAPK (JNK, p38, and ERK) cascades. Additionally, Zhao *et al.* [43] demonstrated that gentiopicroside exhibits a potent protective effect against IL-1β-induced inflammatory responses and enhances Type II Collagen expression by inhibiting the p38, ERK, and JNK branches of IL-1β transduction in rat chondrocytes.

4.2. Gaseous Mediators and Specific Receptor Agonists

Modulating ERK signaling via endogenous gaseous transmitters or specific neuroimmunological receptor pathways represents another innovative pharmacological frontier in OA therapy.

Gasotransmitters have garnered attention for their homeostatic roles; Ha *et al.* [44] investigated the therapeutic efficacy of hydrogen sulfide (H2S) in OA, revealing that H2S markedly reverses the detrimental effects of IL-1β on MMP-13, PGE2, and NO production, alongside suppressing the gene transcription of COX-2, MMP-13, and iNOS. Mechanistically, H2S achieved these effects by directly inhibiting the IL-1β-induced activation of the ERK/IκBα/NF-κB pathway. Concurrently, targeting cholinergic anti-inflammatory pathways has yielded promising results. Liu *et al.* [45] demonstrated that the inhibition of chondrocyte activation can be achieved via the stimulation of alpha-7 nicotinic acetylcholine receptors (α7-nAChRs). Their data indicated that nicotine administration suppresses monoiodoacetate (MIA)- or IL-1β-induced chondrocyte hyperactivation via the α7-nAChR, coupled with a distinct decrease in the resulting phosphorylation of p38,

ERK, JNK, and NF-κB p65.

4.3. Endogenous Biological Factors, Hormones, and Epigenetic Regulators

The therapeutic modulation of the ERK axis can also be orchestrated using endogenous biological proteins, circadian hormones, and epigenetic or enzymatic modulators that dictate joint homeostasis.

Lactoferrin (LF) serves as a prominent marker of neutrophil granulocyte activation, maintaining high concentrations in the synovial fluid of arthritic joints. Zhang *et al.* [46] provided the first evidence demonstrating that LF activates bone morphogenetic protein 7 (BMP7) expression specifically through the ERK pathway, wherein the classical ERK inhibitor U0126 completely abrogates LF-mediated activation of the BMP7 gene in primary articular chondrocytes. Examining circadian hormones, Lim *et al.* [47] analyzed the impact of melatonin in hydrogen peroxide (H_2O_2)-challenged human chondrocytes and rabbit OA models, establishing that melatonin induces cytoprotection and exerts anti-inflammatory effects against H_2O_2-stimulated cytotoxicity, iNOS, and COX-2 via the extensive downregulation of PI3K/AKT, p38, ERK, JNK, and NF-κB signaling.

Conversely, epigenetic and enzymatic targets are critical regulators of this axis. SIRT2, a cytoplasm-localized mammalian sirtuin family member, plays an intriguing role; Eo *et al.* [48] indicated that SIRT2 induction provokes a loss of Type II Collagen, decreases sulfated proteoglycan levels, and incites inflammatory responses by inducing COX-2 and PGE2 expression. Strikingly, the direct inhibition of ERK using PD98059 suppressed SIRT2-mediated dedifferentiation and COX-2 expression in articular chondrocytes. In contrast, viral transduction of lysyl oxidase-like 2 (LOXL2) in OA chondrocytes by Alshenibr *et al.* [49] inhibited chondrocyte apoptosis and upregulated the mRNA levels of chondroitin sulfate proteoglycan (CSPG4), aggrecan (ACAN), SOX9, and COL2A1, while reducing MMP-1, MMP-3, and MMP-13 levels by blunting TGF-β1-induced ERK phosphorylation and IL-1β-induced phospho-NF-κB/p65.

Furthermore, metabolic components and cytokines profoundly interact with this signaling network. Lai *et al.* [50] demonstrated that physiological concentrations of soluble uric acid (sUA) render anti-inflammatory and chondroprotective actions via the inhibition of the ERK/AP-1 signaling axis. Focusing on structural tissues, Xiong *et al.* [51] showed that ERK inhibition exerts therapeutic efficacy against the deleterious degradative effects of the macrophage migration inhibitory factor (MIF)-CD74 signal in human degenerated cartilage endplate (CEP) tissues. Shkhyan *et al.* [52] showed that the drug-induced modulation of glycoprotein 130 (gp130) signaling diminishes apoptosis, hypertrophic differentiation, and cartilage matrix breakdown by suppressing IL-6-mediated activation of ERK and NF-κB cascades. Finally, inhibiting angiopoietin-like protein 2 (aNgPtl2) using specific inhibitors dramatically downregulates inflammation-related gene expressions by halting the phosphorylation of ERK, JNK, p38, AKT, and NF-κB [53], while the novel cytokine IL-37 suppresses pro-inflammatory factor expression via

the IL-1R8 receptor by inactivating p38, ERK, JNK, and NF-κB pathways [54].

4.4. Mechanotransduction and Biomechanical Stress Modulators

Because excessive mechanical loading is a primary physical driver of OA pathogenesis, intervening in mechanotransduction cascades linked to ERK represents a highly physiologically relevant strategy.

Hirose *et al.* [55] reported that excessive mechanical stimulation activates cell-surface integrins (αVβ3 and αVβ5) on chondrocytes, thereby triggering a severe inflammatory cascade that upregulates IL-1β, TNF-α, MMP-3, and MMP-13. Crucially, this mechanical stress-induced acceleration was significantly suppressed by treatment with cilengitide, which acts by blocking the phosphorylation of focal adhesion kinase (FAK) and downstream MAPKs (ERK, JNK, and p38). In the context of high-magnitude cyclic tensile strain (CTS), Sumi *et al.* [56] examined the role of semaphorin 3A (Sema3A), discovering that exogenous Sema3A administration effectively inhibits CTS-upregulated inflammatory cytokine transcription and downregulates the mechanical activation of AKT, ERK, and NF-κB in a dose-dependent manner. Complementing this, Yanoshita *et al.* [57] suggested that FAK directly regulates inflammatory factors such as COX-2, IL-1β, and TNF-α in chondrocytes subjected to CTS by dynamically modulating the phosphorylation of FAK, p38, ERK, and JNK.

4.5. RNA-Based Therapeutics and Advanced Stem Cell-Derived Exosomes

Modern biomedical strategies utilizing non-coding RNAs or stem cell-derived nanovesicles have expanded the therapeutic toolset for precision targeting of the ERK axis in OA.

MicroRNAs serve as critical post-transcriptional regulators of joint cartilage homeostasis. Rasheed *et al.* [58] demonstrated that transfecting chondrocytes with a miR-125b mimic in the presence of IL-1β significantly dampens the secretion of multiple pro-inflammatory cytokines, chemokines, and growth factors—including IL-6, IL-8, INF-γ, IGFBP-1, and PDGF-BB. This broad anti-inflammatory effect was mediated through the inhibition of p38, JNK, and ERK phosphorylation, along with the reduction of nuclear levels of NF-κBp50 and NF-κBp65. Additionally, the therapeutic deployment of cell-free biologicals has emerged as a frontline option; Qi *et al.* [59] analyzed the utility of bone mesenchymal stem cell-derived exosomes (BMSC-Exos) on chondrocyte viability under both physiological and inflammatory settings. Their study demonstrated that BMSC-Exos treatment significantly protects chondrocytes by inhibiting the pathological phosphorylation of p38 and ERK, while concurrently promoting the prosurvival phosphorylation of AKT.

5. Future Research

OA has become one of the major health burdens of the world. Current therapies for OA act only on symptoms and do not prevent the pathogenesis of OA, and the

available therapies are frequently associated with severe side effects. Therefore, researchers have attempted to find effective agents that may inhibit the degeneration and catabolism of articular cartilage. Target-specific treatment may provide a basis for innovative therapeutic approaches in the treatment of OA.

The ERK pathway is ubiquitous and contributes to a myriad of physiological functions, including immune response, cell growth, proliferation, differentiation, and death, among others. Alterations in this pathway play a crucial role in the development and progression of OA. Targeting the ERK pathway might be an innovative approach to the treatment of OA in the future. Optimizing the intensity and duration of this inhibition, as well as the administration route of these compounds, represents a challenge in future preclinical and clinical studies.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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