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Mechanical Signal Transduction: A Key Role of Fluid Shear Forces in the Development of Osteoarthritis

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Abstract: Globally, osteoarthritis is a common and highly disabling disease that places a heavy burden on society and medical systems. The role of biomechanical factors in the development of osteoarthritis has gradually received more attention. As a key biomechanical stimulus, fluid shear force is becoming the focus of research for its dual role in maintaining cartilage health and disease progression. This paper conducts an in-depth discussion on the mechanism of fluid shear force in osteoarthritis and its impact on the disease process, aiming to reveal how fluid shear stress affects the development of osteoarthritis by regulating the physiological function and signal transduction pathways of chondrocytes.

Keywords: fluid shear, osteoarthritis, chondrocytes, signal transduction, biomechanics

Introduction

Osteoarthritis (OA) is a common degenerative joint disease characterized by progressive degeneration of articular cartilage, accompanied by marginal bone hyperplasia[1] and synovial inflammation.[2] The disease is prevalent worldwide, especially among middle-aged and elderly people, seriously affecting patients' quality of life and placing a significant burden on social health care systems.[3]

The causes of OA are complex, including high-risk factors such as aging,[4] trauma,[5] obesity,[6] and high-intensity exercise,[7] which will increase the risk of OA and cause abnormal joint mechanical environment.[8] In OA animal models, experimental models of osteoarthritis (OA) are created by surgery, such as destabilization of medial meniscus (DMM). One of the mechanisms behind this is due to the loss of joint stability, leading to cartilage damage and synovial inflammation, then these changes promote the formation and progression of OA.[9] In recent years, research on the role of biomechanical factors in the pathogenesis of OA has been become research hotspots. Mechanical signals play a key role in the normal physiological and pathophysiological activities of joint cells and tissues. Chondrocytes within bone not only synthesize substances but are also surrounded by specific extracellular matrix (ECM) secreted by them that contributes to low-friction motion of the joint and protects the cartilage tissue when subjected to mechanical stress. In healthy cartilage, exercise-induced mechanical stress is essential to maintain the balance between chondrocyte-led ECM formation and remodeling, which is a continuous and dynamic adjustment process to adapt to the local mechanical environment, involving force perception and transmission. Moderate exercise is necessary to maintain the health of cartilage, as joint inactivity may lead to cartilage degradation.[10] In contrast, excessive mechanical stress is a risk factor for the development and progression of osteoarthritis (OA),[11] a disease that affects the entire joint structure and may eventually lead to loss of joint function.[12] Studies have shown that excessive mechanical loading is actually a dynamic force, which causes cartilage destruction, synovitis, and damage to the extracellular matrix (ECM) through the activation of mechanosensitive cell signaling and the resulting proinflammatory factors and catabolites, leading to uneven joint load distribution.[13] The joint cells and tissues will bear excessive load even under normal physiological pressure, forming

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a vicious cycle (Figure 1). Improving the abnormal mechanical environment by correcting the alignment of the lower limbs can alleviate the progression of OA to a certain extent, such as high tibial osteotomy.

As the main load-bearing part of the mobile joint, articular cartilage plays a very important role in supporting and protecting the joint by minimizing friction and wear and ensuring the uniform transmission of the load on the cartilage surface to the lower bone of the cartilage. Subchondral bone and articular cartilage must coordinate to resist sufficient friction and mechanical stress.[14] The articular cartilage has a specific structure for low friction movement and load-bearing. Articular cartilage is structurally divided into two layers: calcified and non-calcified, which are separated by a clear boundary, the tide mark. The uncalcified layer can be further divided into three sub-layers: superficial layer, middle layer, and deep layer.[15] The deep layer is mainly subjected to compression load, the middle layer is subjected to compression force and fluid shear force, and the surface layer is mainly subjected to fluid shear force[16] (Figure 2). It was found that in the early stage of OA in mice, the elastic modulus of the most surface of articular cartilage (about 1 micron thickness) is significantly reduced before the histological phenotype of cartilage damage has emerged,[17] and this reduction is due to the decreased anabolic metabolism of the surface cells of cartilage after injury stimulation, such as decreased proliferation and differentiation, decreased expression of collagen type II (Col-II) and Aggrecan, and increased catabolism. The increase of apoptosis and hypertrophy, as well as the expression of extracellular matrix-degrading enzymes (MMPs), lead to the loss of surface cells and cartilage degradation, resulting in the disorder of cartilage metabolism and the gradual formation of irreparable defects.[18] It is suggested that in the early stage of OA, the surface cells of cartilage are damaged, with decreased anabolism and increased catabolism, leading to the degradation and destruction of the extracellular matrix of cartilage. Superficial chondrocytes are mainly subjected to fluid shear stress, so there is an urgent need to study the potential mechanism of fluid shear stress-induced OA.

Fluid shear stress, as an important biomechanical stimulus, has a significant impact on the physiological function and signal transduction pathways of chondrocytes. It has been found that low levels of shear stress (less than 5 dyne/cm2) have a protective effect on cartilage. However, when shear stress increases to a higher range (10–20 dyne/cm2), it induces the

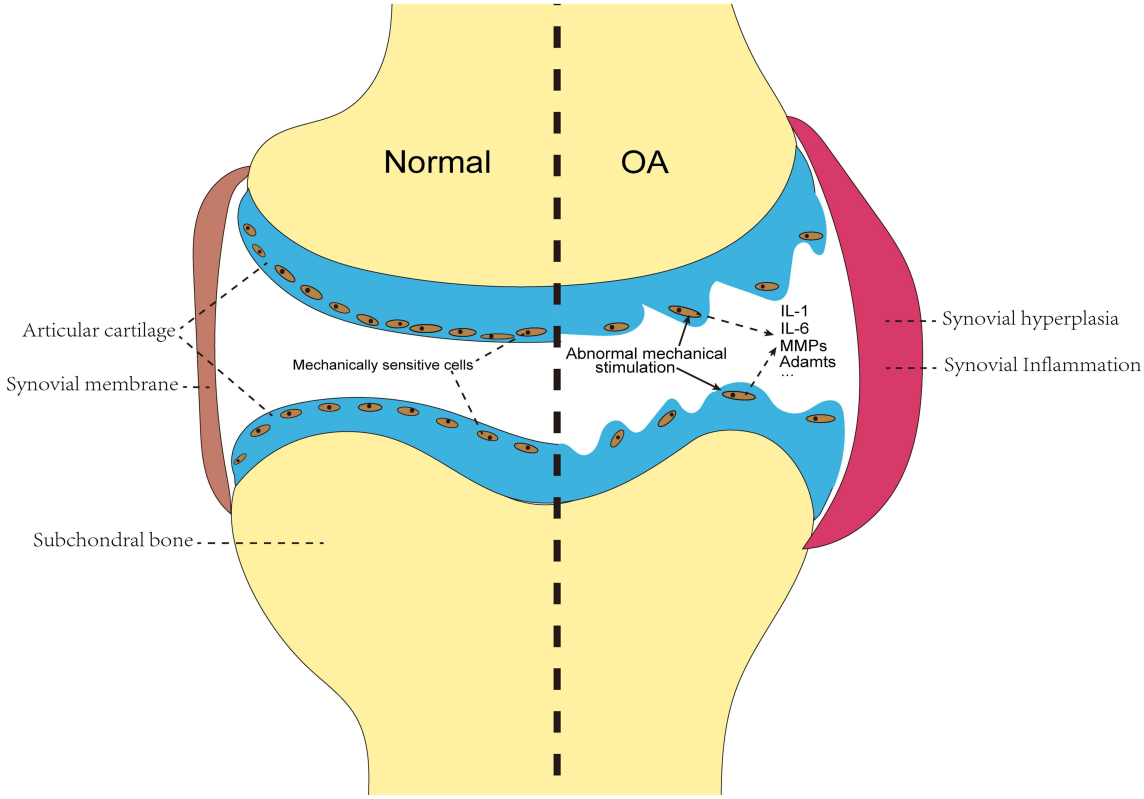

Figure 1 The left half illustrates the structure of a normal synovial joint. The right side depicts abnormal mechanical stimulation leading to alterations in the synovial joint structure, a process mediated by mechanically sensitive cells.

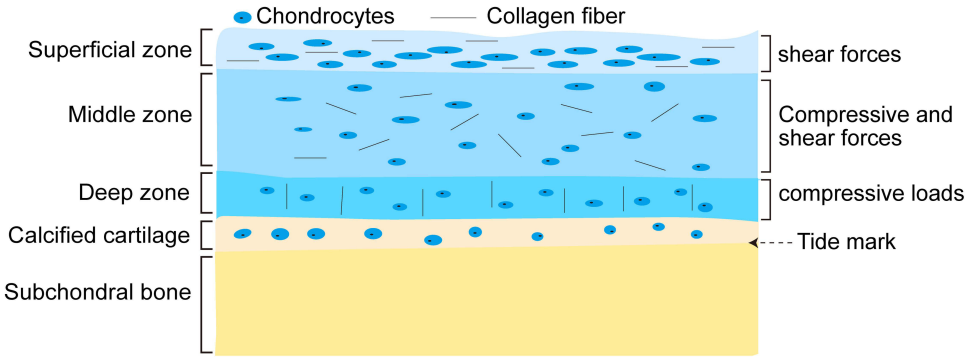

Figure 2 The articular cartilage has a four-layer structure, which from superficial to deep consists of: the superficial zone, the middle zone, the deep zone, and the calcified zone.

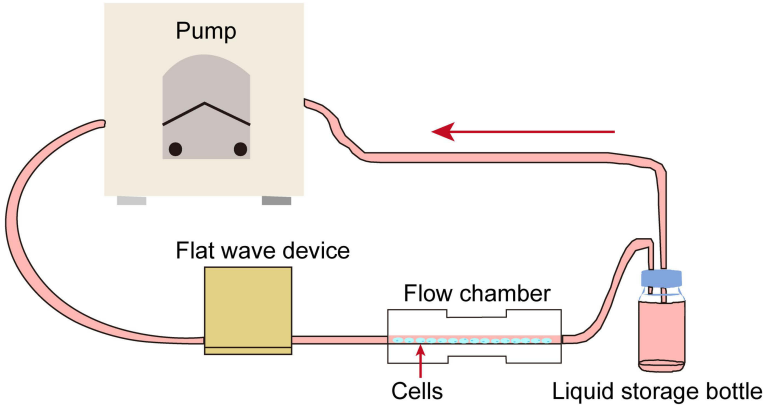

Figure 3 Schematic representation of in vitro simulated cellular fluid shear stress.

expression of inflammatory factors and matrix degrading enzymes, which eventually leads to the breakdown of matrix and osteoarthritis-like changes.[19] In a constant knee joint cavity, the fluid shear stress on the articular cartilage tissue is related to the viscosity of the synovial fluid and the volume of fluid passing through the articular cartilage per unit time, calculated according to the fluid shear force formula: $\tau=6\ \mu Q/WH2$ (μ is the dynamic viscosity of the perfusion fluid, Q is the flow rate, W is the width, H is the channel height),[19] A schematic diagram of fluid shear stress applied to cells in vitro can be seen in Figure 3. The joint fluid flow velocity is increased when running with high intensity and large amount of exercise. Clinically, it is found that the viscosity of joint cavity fluid in advanced OA patients is higher than that in normal people (early OA patients). These results suggest that different fluid shear forces play different roles in normal and OA cartilage. This article aims to review the signal pathways of fluid shear stress activated signal transduction in chondrocytes and the role, function, clinical significance and potential therapeutic targets of key signal molecules.

Signaling Pathways and Key Signaling Molecules

Chondrocytes respond to fluid shear stress through a variety of mechanisms, including ion channel activation, integrin-mediated focal adhesion signaling, and G protein-coupled receptor signaling.[20,21] Fluid shear stress induces the rapid release of intracellular calcium ions and adenosine triphosphate (ATP), which initiates the generation of second messengers such as nitric oxide (NO) and prostaglandins,[22–24] thereby regulating numerous cell signaling pathways and promoting the diversification of cell functions (Table 1).

Wnt Signaling Pathway

The Wnt signaling pathway is an intercellular signaling chain activated by modified lipid proteins secreted by the Wnt family. The most basic components of the pathway include Wnt ligands released by the secretory cells, matching

Table 1 Signaling Pathways and Key Signaling Molecules

Signaling pathways	Wnt signaling pathway TGF- signaling pathway NF-κB signaling pathway AMPK signaling pathway Hippo signaling pathway
Key signaling pathways	Col-II, Col-X, COX-2, IL-6 Adamts-4, Adamts-5, MMP13

receptors on the surface of the receiving cells, and signal transduction molecules in the receiving cells.[25] Wnt signaling plays a key role in the process of bone formation, including chondrogenic differentiation, chondrocyte hypertrophy, growth plate chondrocyte organization and osteoblast differentiation and maturation, through paracrine and autocrine ways.[26] It has been found that moderate Wnt signaling activation is necessary to maintain the health of articular cartilage, and inactivation of the Wnt signaling pathway leads to degradation of articular cartilage and chondrocyte apoptosis.[27] The excessive activation of Wnt signaling promotes the progression of OA, and β-catenin is significantly up-regulated in articular surface chondrocytes of OA mice.[28]

Jin et al found that Wnt signaling was strongly activated when chondrocytes were treated with high fluid shear stress, and inhibition of Wnt/β-catenin by the specific Wnt/β-catenin inhibitor LF3 could alleviate the damaging effect of FSS on primary chondrocytes, as shown by increased levels of COLII and SOX9. COX-2 and MMP13 levels were decreased.[19] Dole et al found that the inhibition of miR-100 attenuated Wnt signaling induced by FSS (10 dyne/cm2) and TGFβ. miR-100 antagonated Wnt signaling by targeting and inhibiting the expression of frizzled receptor (FZD5/FZD8), leading to degradation of cartilage matrix and aggravate chondroblastic damage, and promote the pathological process of OA.[29]

Current studies mainly focus on the effect of high fluid shear stress on chondrocytes. However, whether low fluid shear stress protects chondrocytes by moderately activating Wnt signaling pathway may involve promoting the proliferation of chondrocytes, maintaining the synthesis of cartilage matrix, and inhibiting inflammatory response, but the specific mechanism is still unclear. In addition, there is a lack of quantitative studies on the extent of Wnt signaling activation, which is crucial for understanding its role in the physiological and pathological processes of chondrocytes. Especially in the early intervention and treatment of osteoarthritis, understanding and controlling the activation level of Wnt signaling pathway may provide new strategies for delaying disease progression.

TGF-β Signaling Pathway

TGF-β (transforming growth factor-β) is a multifunctional cytokine, which activates Smad proteins by binding to its receptor, and subsequently translocate to the nucleus and regulate the expression of target genes.[30] TGF-β signaling pathway plays an important role in the development, maintenance and disease process of articular cartilage. It has a significant impact on the proliferation, differentiation, apoptosis of chondrocytes, and the synthesis and degradation of extracellular matrix.[31] It has been found that TGF-β signaling plays a double-edged sword role in articular cartilage health and disease. In physiological states, it has a positive effect on the synthetic activity of chondrocytes and inhibition of apoptosis, while in pathological states such as OA, its abnormal activation may lead to degenerative changes in cartilage.[32]

Malaviya et al found that fluid shear stress stimulated the proliferation of chondrocytes mediated in part by TGF-β.[33] David et al found that fluid shear stress is sufficient to activate TGFβ signaling even in the absence of additional TGF-β by causing rapid phosphorylation and nuclear translocation of Smad proteins activated by TGF-β.[34] Current studies have shown that fluid shear stress activates TGF-β signaling pathway, and the role of TGF-β signaling pathway is complex. On the one hand, TGF-β can combat the progression of OA by promoting cartilage repair and inhibiting inflammatory response. On the other hand, abnormal activation of TGF-β signaling is associated with degenerative changes in cartilage

and may lead to abnormal differentiation of chondrocytes and degradation of cartilage matrix. Especially in the late stages of OA, the imbalance of TGF-β signaling pathway may aggravate cartilage destruction and joint inflammation. However, there is a lack of research on whether high fluid shear stress leads to abnormal activation of TGF-β signaling pathway and whether low fluid shear stress promotes cartilage repair and inhibits inflammation partly by activating TGF-β signaling pathway. These findings will provide new insights into understanding how fluid shear stress regulates chondrocyte function by affecting TGF-β signaling and provide possible directions for the development of novel therapeutic strategies.

NF-κB Signaling Pathway

NF-κB is a multifunctional transcription factor involved in the regulation of a variety of cellular responses, including inflammatory response, cell proliferation, differentiation, and apoptosis.[35] The NF-κB family includes five members: RelA/p65, RelB, c-Rel, NF-κB1/p50 (p105), and NF-κB2/p52 (p100). All of these proteins contain an N-terminal Rel homology domain (RHD), which is evolutionarily conserved and helps in the dimerization of protein complexes, nuclear localization, DNA binding, and interaction with NF-κB inhibitors.[36] In articular cartilage, the activation of NF-κB signaling pathway is closely related to the metabolism of chondrocytes. In the physiological state, NF-κB is involved in normal cartilage development and maintenance of chondrocyte function. However, in pathological conditions, such as OA, abnormal activation of NF-κB is associated with enhanced catabolism of chondrocytes, increased apoptosis, and degradation of cartilage matrix.[37–39] These changes eventually lead to degenerative changes in articular cartilage and joint dysfunction.

Shun et al found that induction of Kruppel-like factor (KLF4) in human chondrocytes under 2dyn/cm² shear stress attenuated interleukin (IL) −1β-stimulated activation of nuclear factor-κb.[40] Studies have shown that fluid shear stress activates the NF-κB signaling pathway by activating mechanosensitive receptors on the surface of articular cartilage. Different degrees of fluid shear stress have different effects on cartilage, and NF-κB signaling pathway plays different roles in different physiological and pathological stages of cartilage development, formation and injury, showing a complex action mode of NF-κB signaling pathway. Future studies are needed to further elucidate the specific mechanisms of interaction between fluid shear stress and NF-κB signaling and how these interactions affect articular cartilage health and disease progression.

AMPK Signaling Pathway

Adenosine monophosphate (AMP)-activated protein kinase (AMPK) is a heterotrimeric complex consisting of a catalytic subunit α and two regulatory subunits β and γ.[41] AMPK is an energy-sensing enzyme that plays a key role in cellular energy balance and metabolic regulation.[41] When cellular energy is low, Thr172 in the α subunit is phosphorylated, leading to the activation of the AMPK complex.[41] In articular chondrocytes, AMPK signaling pathway may be involved in regulating the metabolic activity of chondrocytes and the response to mechanical stimulation. Mechanoactive ion channels, such as Piezo1, Piezo2 and TRPV4, regulate Ca^{2+} influx into cells and initiate Ca^{2+} signaling, which interact with MAPKs to cause changes in cartilage metabolism.[42,43] Although data on direct effects of fluid shear stress on articular cartilage via AMPK signaling pathway are limited, it can be speculated that as an intracellular energy-sensing enzyme, AMPK may be involved in regulating the metabolic response of chondrocytes to fluid shear stress stimulation. For example, fluid shear stress may affect the metabolic state and anabolic pathways of chondrocytes by altering intracellular ATP levels or directly activating AMPK, which in turn affects cartilage health and function. Future studies can further explore the specific role of this pathway in the response of articular cartilage to fluid shear stress.

Hippo Signaling Pathway

The Hippo signaling pathway is an evolutionarily conserved signaling pathway, at the core of which is a kinase cascade consisting of mammalian Ste20-like kinase 1 (MST1; also known as STK4), MST2 (also known as STK3), the adaptor protein Salvador 1 (SAV1), large tumor suppressor kinase 1 (LATS1), LATS2, MOB kinase activator 1A (MOB1A) and 1B (MOB1B), the homologous transcriptional co-activator YAP and the transcriptional co-activator with PDZ-binding motif (TAZ), as well as the TEAD family of transcription factors (TEAD1-TEAD4).[44] The Hippo signaling pathway is

a key regulatory network for cell growth and organ size. Recent studies have shown that it also plays an important role in the physiological and pathological processes of articular cartilage.[45] In articular cartilage, Hippo signaling mainly acts through its downstream effectors Yes-associated protein (YAP) and TAZ (transcriptional coactivator and PDZ-binding motif). After the activation of the Hippo pathway, a series of phosphorylation processes inhibit the nuclear translocation of YAP and TAZ, leading to their degradation in the cytoplasm. When the Hippo pathway is not active, YAP and TAZ enter the nucleus to bind to transcription factors and promote gene transcription. In OA cartilage, the expression level of YAP is increased and correlated with the degree of joint damage.[46] Overexpression of YAP resulted in increased expression of catabolic genes, while inhibition of YAP reduced IL-1β-induced catabolic gene expression and chondrocyte apoptosis.[47] A recent study revealed that YAP/TAZ are dispensable for chondrocyte differentiation and endochondral ossification,[48] and the role of Hippo/YAP pathway in cartilage development is dynamic. In summary, the role of Hippo signaling in chondrogenesis is controversial. Further research is needed.

Zhong et al found that with the increase of fluid shear stress, the expression of YAP was enhanced, which eventually led to the dedifferentiation of chondrocytes and the loss of chondrocyte properties.[49] At present, the research mainly focuses on the effect of mechanical load on the expression of YAP, and then on cartilage metabolism.[46] However, the research on fluid shear stress as a part of mechanical load is relatively few. Different fluid shear stress has different effects on cartilage. The role of Hippo signaling pathway is also controversial, which may be due to the dominant role of upstream signals or downstream target genes in this pathway under different fluid shear stress, and there is a complex interaction between Hippo/YAP and other signaling pathways. Understanding how fluid shear stress regulates the biological processes of articular cartilage through the Hippo signaling pathway is important for the development of new therapeutic strategies. Future studies are needed to further clarify the specific mechanism of Hippo signaling pathway in the response of articular cartilage to fluid shear stress.

Key Signaling Molecules

Fluid shear stress regulates multiple signaling pathways by activating mechanosensitive receptors on the surface of cartilage, leading to the expression or inhibition of downstream target genes, and indirectly affecting the metabolism and phenotype of chondrocytes.

Gemmiti et al observed a significant increase in collagen type II (COL-II) expression when chondrocytes were subjected to fluid shear stress of 1dyn/cm² for 3 days.[50] Similarly, Bao et al reported in their study that COL-II expression level was significantly increased when chondrocytes were exposed to 0.05 dyn/cm² fluid shear stress for 7 days compared with the control group.[51] Yokota et al found that the expression level of matrix metalloproteinase 13 (MMP13) was decreased when human chondrocytes were subjected to 5dyn/cm² shear stress, but increased when human chondrocytes were subjected to higher fluid shear stress (20dyn/cm²).[52] However, Jin et al found that the expression level of COL-II was significantly reduced after chondrocytes were subjected to high fluid shear stress for 2 hours.[19] When chondrocytes were exposed to a high level of fluid shear stress (20 dyn/cm²) for 2 h, MMP13, ADAMTS4, ADAMTS5, cyclooxygenase-2 (COX-2) and interleukin-6 (IL-6) expression levels were significantly increased in these cells.[51] These results suggest that prolonged low fluid shear stress can promote chondrocyte anabolism, while short time high fluid shear stress can promote chondrocyte catabolism.

Carter et al found that low fluid shear stress inhibited cartilage hypertrophy, whereas high fluid shear stress promoted cartilage hypertrophy.[53] After Jin et al applied high fluid shear stress to chondrocytes, hypertrophy related markers such as COL-X and COX-2 were significantly up-regulated.[19]

Discussion

As a mechanical signal, fluid shear stress has a significant impact on the biological behavior of articular chondrocytes. In articular cartilage, moderate fluid shear stress is essential to maintain the physiological function of chondrocytes and the homeostatic balance of cartilage matrix. However, excessive or sustained shear stress may lead to pathological changes in chondrocytes, such as inflammation, matrix degradation and apoptosis, which are key factors in the development of osteoarthritis (OA). Therefore, understanding how fluid shear stress affects chondrocytes through specific signaling pathways and key signaling molecules is important to reveal the pathogenesis of OA.

The activation and inhibition of signaling pathways play a central role in the response of chondrocytes to fluid shear stress. For example, signaling pathways such as Wnt, TGF-β, and NF-κB play an important role in regulating the inflammatory response, cell proliferation, and apoptosis of chondrocytes. Abnormal activation of these pathways may lead to chondrocyte dysfunction, which in turn promotes the progression of OA. Therefore, investigating the regulatory mechanisms of these signaling pathways in OA may provide targets for the development of new therapeutic strategies. The role of key signaling molecules such as COX-2, IL-6, MMPs and ADAMTS family members in the process of cartilage degeneration cannot be ignored. The expression and activity of these molecules are regulated by fluid shear stress, and their abnormal expression is closely related to the degradation of cartilage matrix and the pathological process of OA. Therefore, in-depth study of the role of these signaling molecules in OA will help to better understand the molecular mechanisms of cartilage degeneration and may provide new biomarkers and therapeutic targets for clinical treatment.

Although current studies have revealed some key mechanisms of fluid shear stress in OA development, many questions remain to be addressed. For example, how different intensity and duration of fluid shear stress affect the long-term behavior of chondrocytes, how these effects interact with the individual's genetic background and environmental factors, and the crosstalk between signaling pathways are questions that need to be addressed in future studies. In addition, the previous research mainly focused on cartilage tissue, while there were few studies on the mechanics of synovial tissue, especially the synovial cells directly adjacent to the joint surface to sense the changes of joint mechanical signals, including fluid shear force and friction force on the synovial surface, leading to changes in the biological function of synovial cells. The development of drugs to improve osteoarthritis induced by fluid shear force through mechanotransduction is a key area for future research. For example, Jia et al developed an injectable thermosensitive hydrogel that releases ApoE antagonists at the fracture site, which effectively alleviates the aging of chondrocytes. The specific absence of Piezo1, a mechanically sensitive ion channel, in chondrocytes upregulates the expression of apolipoprotein E (ApoE) in hypertrophic chondrocytes.[54] Xie et al injected a biomimetic cartilage-lubricating polymer into osteoarthritic joints induced in rats by surgery, leading to cartilage regeneration and the elimination of osteoarthritis within 8 weeks.[55] The intra-articular injection of drugs not only protects chondrocytes but also alters the viscosity of the joint cavity fluid, resulting in changes to the fluid shear forces experienced by the chondrocytes. Finally, therapeutic intervention strategies targeting the signaling pathways and key signaling molecules caused by fluid shear stress require further experimental validation and clinical trials to evaluate their safety and efficacy.

Taken together, fluid shear stress plays an important role in OA development by affecting key signaling pathways and molecules. Future research is needed to understand these complex biological processes at a deeper level and explore new therapeutic strategies in order to bring better treatment outcomes for OA patients.

Conclusion

Fluid shear force acts as a mechanical stimulus to maintain homeostasis in the joint. The recognition and response of chondrocytes to fluid shear stress is a key factor that determines their phenotypic properties, regulates the inflammatory process, and finely regulates the balance between synthesis and catabolism, which is extremely important for maintaining the normal health of cartilage. Chondrocytes adapt to fluid shear stress through multiple mechanosensing mechanisms and signaling pathways. Future studies are needed to further elucidate how these signaling pathways and molecules are precisely regulated by fluid shear stress. To translate this understanding into clinical applications, we can establish in vitro and in vivo models to study the effects of fluid shear stress on chondrocyte function and cartilage health, and to test the efficacy of potential therapeutic interventions. Additionally, we can investigate the potential of biomechanical interventions, such as joint unloading or physical therapy, to modulate fluid shear stress and alleviate osteoarthritis (OA) symptoms. Furthermore, we can explore the use of pharmacological agents that can mimic or enhance the effects of fluid shear stress on chondrocyte biology and cartilage health. Through a deeper understanding of the mechanism of fluid shear stress in OA, we can expect to develop new therapeutic strategies that will provide more effective treatment options for OA patients and improve their quality of life.

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Disclosure

The authors report no conflicts of interest in this work.

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