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Review Article

The relationship between biomechanical factors and intervertebral disc degeneration: a review

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Abstract: The intervertebral disc is an avascular structure composed of the nucleus pulposus, annulus fibrosus, and the superior and inferior cartilage endplates. Located between adjacent vertebrae, it connects them structurally, contributing to spinal stability, load-bearing, shock absorption, and protection of the spinal cord. Intervertebral disc degeneration (IDD) results from various factors, including mechanical overload, trauma, repetitive strain, pregnancy, genetic predisposition, and developmental abnormalities. In the context of increased occupational demands and lifestyle changes, the spine is subjected to greater biomechanical stress, accelerating disc degeneration; increasing the risk of lumbar disc herniation. This review summarizes current knowledge on how biomechanical factors contribute to IDD, focusing on the involvement of mechanical stimuli in cellular and molecular pathways. It highlights both the detrimental and potentially protective effects of biomechanical forces on intervertebral discs and their resident cells. By exploring the dual roles of these forces, this review aims to inform future research directions and therapeutic strategies. Taken together, the evidence underscores a strong relationship between biomechanical loading and intervertebral disc degeneration at both the tissue and cellular levels.

Keywords: Biomechanical factors, intervertebral disc degeneration, nucleus pulposus, pathway

Introduction

Current studies have yet to fully elucidate the etiology and progression of intervertebral disc degeneration (IDD), which is driven by multiple factors [1]. This review focuses on the impact of biomechanical forces on intervertebral discs and their cellular components. Biomechanical factors encompass various mechanical stimuli, including compression, tension, and mechanical stress, each of which can contribute to disc degeneration through distinct mechanisms.

For example, tensile stress can induce endoplasmic reticulum stress (ERS), thereby promoting disc degeneration [2]; compressive loading has been shown to trigger nucleus pulposus (NP) cell senescence via activation of the p38 MAPK pathway [3]; and mechanical tension promotes inflammasome expression in annulus fibrosus (AF) cells, reducing their structural integrity [4]. Additionally, abnormal mechanical loading can lead to overactivation of transforming growth factor-β (TGF-β), resulting in endplate sclerosis [5].

Given the multifactorial nature of disc aging, this review also explores the roles of various molecular pathways and substances in delaying disc degeneration. The intervertebral disc is an avascular structure located between vertebral bodies and relies on diffusion from adjacent capillaries at the vertebral endplates for nutrient supply [6]. Mechanical stress can impair this nutrient transport, further exacerbating degeneration. For example, mechanical traction may hinder nutrient diffusion through the endplates [7].

As the intervertebral disc is subjected to daily biomechanical loading, these forces exert both harmful and protective effects. Low-magnitude mechanical loading can enhance β-catenin expression, potentially promoting tissue repair [8], while high-magnitude stress may directly damage disc tissues [9]. Thus, understanding

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the dual roles of mechanical forces may reveal mechanisms underlying IDD and identify potential therapeutic targets [10].

The NP primarily consists of proteoglycans, chondrocytes, water, and type II collagen. It functions to evenly distribute mechanical loads to the adjacent endplates and maintain tension within the AF [1]. The cartilage endplate (CEP), located between the disc and vertebral body, serves as a critical interface for nutrient exchange [11] and is highly sensitive to biomechanical influences. Excessive loading may reduce its transport capacity [7], induce calcification of endplate chondrocytes [12], and promote cartilage degradation via upregulation of matrix metallopeptidase 13 (MMP13) through NF-κB signaling activation [13].

In summary, the intervertebral disc, as a structural bridge between vertebrae, is subjected to diverse mechanical forces that can irreversibly impact its structure and cellular function through various molecular pathways. As disc degeneration is a major contributor to low back pain, it is essential to investigate the mechanobiological interactions affecting the disc and its constituent cells. This review first examines biomechanical influences at the macro level, then delves into their specific effects on the NP, AF, and CEP at the micro level. By addressing both the detrimental and protective roles of biomechanical forces, we aim to offer new perspectives and strategies for delaying disc degeneration.

Relationship between biomechanical factors, signaling pathways, and IDD

Damaging mechanism of biomechanics on the intervertebral disc

Mechanical stress is one of the most significant and prevalent contributors to IDD. This section summarizes the negative effects of mechanical loading and associated signaling pathways on the intervertebral disc at a macroscopic level.

In vitro, compressive loading promotes the release of lactate dehydrogenase and prostaglandin E2 (PGE2), and activates the extracellular signal-regulated kinase 1/2 (ERK1/2) MAPK pathway, contributing to disc degeneration [14]. Prolonged compression activates the p53-mediated mitochondrial apoptotic pathway, leading to increased pro-apoptotic proteins and decreased anti-apoptotic proteins, which ultimately result in cell death and disc degeneration [15]. Additionally, excessive mechanical stress disrupts circadian rhythms via the Rho/ROCK pathway by impairing the transcription of core clock proteins, which in turn contributes to IDD. Targeting this mechanism may benefit individuals exposed to shift work or chronic nighttime activity [16].

Degeneration mechanisms also differ between dynamic and static loading. Dynamic loading causes widespread cell death within the intervertebral disc, whereas static loading predominantly affects the outer annulus fibrosus. Nevertheless, both loading types can induce lumbar venous malformations within 21 days in animal models [17]. Similarly, low cyclic tensile forces primarily deform the inner disc wall, while high cyclic tensile forces damage the middle layer of the disc [18]. Cyclic mechanical tension induces ERS and subsequently triggers autophagy via the reactive oxygen species (ROS) pathway, ultimately accelerating disc tissue degeneration [2]. In rabbit models, supraphysiological shear stress can initiate IDD, and prolonged exposure may lead to lumbar spondylolisthesis and progressive disc degeneration [19].

The duration of mechanical stress also plays a critical role. Daily compression for 8 hours significantly reduces NP cell viability. With prolonged compression, MMP13 expression is further suppressed; however, a certain threshold of mechanical stress may still promote extracellular matrix (ECM) synthesis, whereas excessive stress exerts detrimental effects on disc cells [9]. An overview of these mechanisms is illustrated in **Figure 1**.

Protective mechanism of biomechanical factors on the intervertebral disc

Biomechanical stimuli and related pathways exhibit dual roles in modulating disc health. While mechanical loading can induce degeneration, under certain conditions it can also activate protective responses. For example, although compression triggers mitochondrial apoptosis, hypoxia in the degenerative disc microenvironment activates the HIF-1α/YAP signaling pathway, which enhances the survival

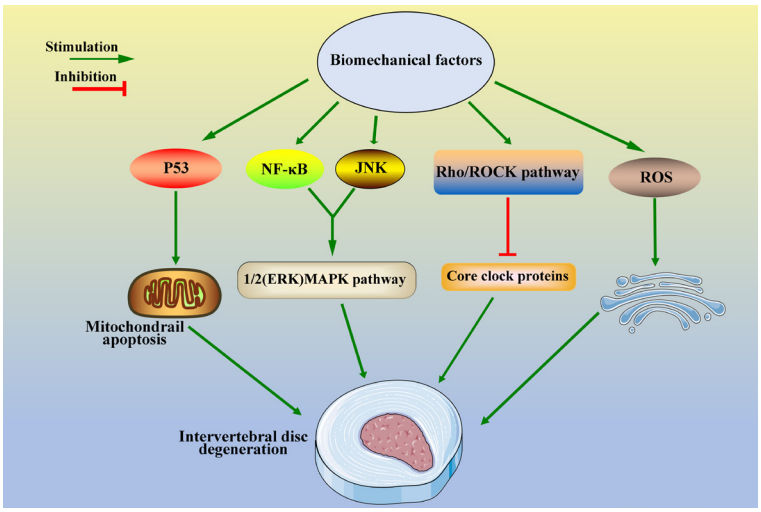

Figure 1. At the macro level, biomechanical factors directly lead to intervertebral disc degeneration through different mechanisms such as P53 leading to mitochondrial apoptosis, activation of reactive oxygen species leading to endoplasmic reticulum autophagy, JNK activating specific pathways, or affecting protein expression through pathways.

of bone marrow mesenchymal stem cells and mitigates compression-induced apoptosis [20].

MitoQ, a mitochondria-targeted antioxidant, alleviates mitochondrial dysfunction and oxidative stress by restoring mitochondrial dynamics, enhancing mitochondrial-lysosomal fusion, and improving lysosomal function. It also upregulates Nrf2 activity to reduce compression-induced disc degeneration [21].

Mechanical stress can also activate TGF-β through integrin-mediated signaling, which regulates endothelial cell function and maintains tissue homeostasis - offering a potential therapeutic target [22]. The NEMO-binding domain (NBD) peptide has been shown to reduce NP and AF damage under compressive force, enhance cell viability, and protect disc tissue in rat models [23].

Manual therapy (MT), a traditional treatment for discogenic pain, has been demonstrated to reduce oxidative stress via the SIRT1/FOXO1 pathway. MT increases the expression of SIRT1 and FOXO1, decreases acetylated FOXO1 (Ac-FOXO1), modulates aging-associated markers such as β-galactosidase, p53, p21, p16, and telomerase activity, and improves disc mobility - suggesting that non-invasive, drug-free interventions may help delay disc aging [24].

Additionally, mechanical stress enhances the expression of β-catenin, a Wnt pathway transcription factor, in disc tissue. This upregulation appears to mediate regenerative responses, offering another promising strategy for treating IDD [8].

Relationship between biomechanical forces and NP cells of the intervertebral disc

Detrimental effects of biomechanical stress on NP cells

Influence of stress intensity and duration: The impact of mechanical stress on NP cells varies depending on its intensity and duration, and can generally be classified into two categories: moderate, physiological stress, and excessive, pathological stress. Moderate mechanical stimulation activates the FAK-MEK5-ERK5-c-Fos-AP-1 signaling cascade. Activated AP-1 inhibits the expression of collagenase and matrix metalloproteinases (MMPs), thereby regulating the synthesis of type II collagen, proteoglycans, and cytoskeletal-associated proteins (MAP-1, MAP-2, MAP-4), which contributes to cytoskeletal remodeling and tissue homeostasis [25].

In contrast, excessive cyclic mechanical strain (CMS), particularly low-frequency, high-amplitude CMS, activates the p65 subunit of NF-κB in human NP cells. Overexpression of p65 promotes degenerative changes, suggesting that high-amplitude, low-frequency CMS exacerbates NP cell degeneration via the p65 pathway [26].

Effect of mechanical stress on NP cells: Excessive mechanical loading is a major contributor to IDD. It induces the expression of Piezo1, a mechanosensitive ion channel, which promotes NP cell senescence, nucleus pulposus sclerosis, and the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. These changes collectively accelerate NP cell apoptosis and reduce ECM synthesis, compromising cell viability [27]. Moreover, increased

ECM stiffness enhances Piezo1 expression, elevating intracellular Ca^{2+}, ROS levels, and markers of ERS such as GRP78 and CHOP, ultimately leading to apoptosis [28].

Mechanical stress also suppresses Kindlin-2 expression. Loss of Kindlin-2 activates the NLRP3 inflammasome and increases IL-1β expression in NP cells, establishing a vicious inflammatory cycle that accelerates IDD progression [29]. Additionally, 4 hours of rest following 20 hours of mechanical loading fails to restore NP cell viability and instead activates NF-κB signaling, further promoting ECM degradation and apoptosis [30]. The RhoA/MRTF-A nuclear translocation pathway, triggered by mechanical stress, increases fibrotic activity in NP tissue [31].

Effect of compression on NP cells: Compression is a classical biomechanical factor involved in IDD. In rat NP cells, compression induces autophagy via suppression of the ROS-dependent PI3K/AKT/mTOR and ROS-independent JNK pathways, with JNK expression increasing proportionally with compression duration [32]. In human NP cells, compression activates the RhoA/ROCK1 pathway, enhancing myosin IIA-actin interaction and inhibiting myosin IIB-actin binding, which promotes cellular senescence. Actin cytoskeleton remodeling and MRTF-A nuclear translocation also contribute to fibrosis [33].

High-amplitude compression (1.3 MPa, 1.0 Hz) increases expression of senescence markers including β-galactosidase, p16, and p53, and decreases PCNA levels, in part via p38-MAPK activation [34]. High hydrostatic pressure triggers apoptosis through activation of the Hippo-YAP/TAZ pathway, accelerating ECM breakdown [35]. The PINK1/Parkin pathway is also activated under compression, promoting mitophagy and cell senescence in a time-dependent manner. Inhibition of this pathway with PINK1-shRNA significantly reduces senescence [36].

Compression also upregulates Drp1, promoting mitochondrial translocation of p53 and nuclear translocation of AIF, which results in programmed necrosis [37]. In addition, compression enhances ERS and ER-mitochondria interactions, leading to mitochondrial calcium overload and further necrosis [38]. Downregulation of circRNA-CIDN under compression disrupts ECM homeostasis and induces NP cell apoptosis [39].

Prolonged compression reduces the expression of N-cadherin and NP-specific markers such as Brachyury, Laminin, and Glypican-3, decreases glycosaminoglycan and hydroxyproline content, and impairs ECM synthesis [40]. In contrast, short-term static loading promotes type II collagen synthesis, while sustained compression impairs proteoglycan production [41]. These mechanisms are illustrated in **Figure 2**.

Effect of fluid shear stress on NP cells: Fluid shear stress arises from opposing forces acting tangentially on the same structure and can be transmitted to NP cells within the disc. Like other mechanical stimuli, moderate shear stress supports ECM balance. It promotes autophagy in NP cells, as evidenced by increased LC3-II, decreased LC3-I, elevated Beclin-1, and enhanced formation of autophagosomes and autolysosomes, primarily via HO-1 activation [42].

Shear stress also upregulates numerous proteins [43], including CCN1, which regulates cell proliferation, differentiation, senescence, apoptosis, and cartilage and bone formation through various pathways [44]. Moreover, it enhances S100A7 expression and promotes osteoclast differentiation by stimulating monocytes [45].

Effect of cyclic mechanical tension on NP cells: Cyclic mechanical tension refers to rhythmic, time-dependent mechanical stimuli. Its effects on NP cells are dual in nature. On one hand, it promotes NP cell proliferation and cell cycle progression, reduces apoptosis, and ameliorates degeneration by regulating the ITGA2/PI3K/AKT signaling pathway and enhancing COL2A1 expression [46]. Notably, siRNA-mediated knockdown of integrin α1 impairs COL2A1 expression under cyclic tension [47]. This type of loading also activates the Src-GIT1-ERK1/2 pathway, supporting ECM production and physiological function in NP cells [48].

On the other hand, excessive cyclic tension induces DNA damage, apoptosis, and activation of the p53-p21-Rb pathway [49]. It also elevates the expression of zinc transporters (e.g., ZIP8) and matrix-degrading enzymes (e.g.,

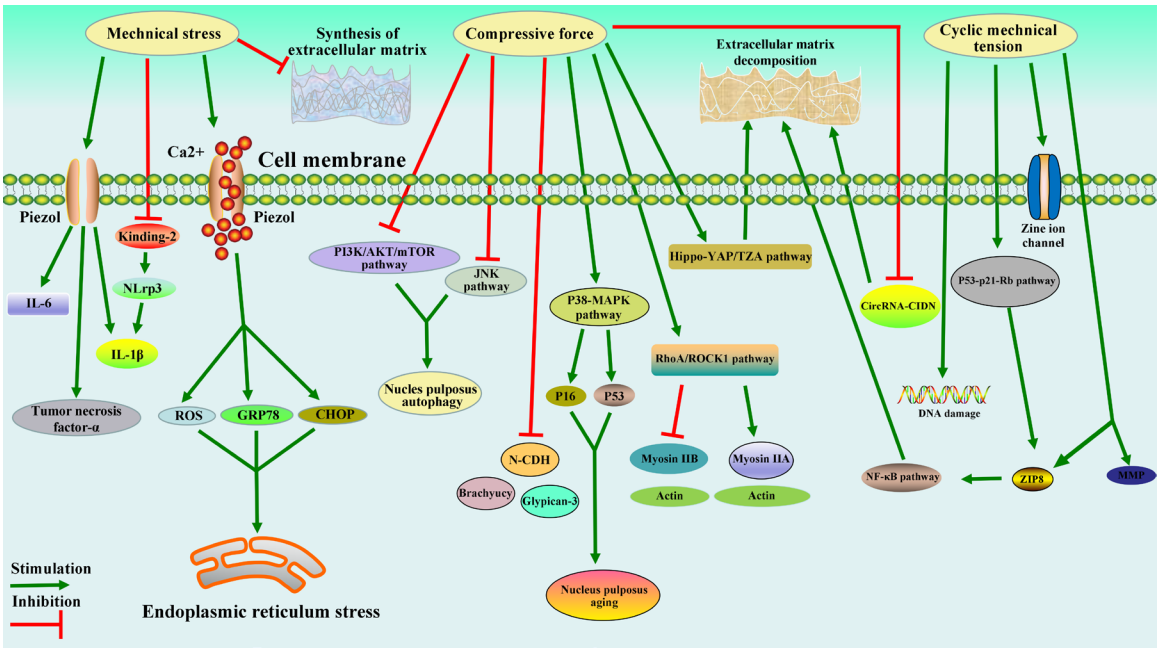

Figure 2. Under the influence of mechanical stress, it can directly inhibit the synthesis of extracellular matrix, activate the mechanically sensitive ion channel Piezo1 on the nucleus pulposus cell membrane, not only promote the production of IL-6, IL-1β, and tumor necrosis factor-α, but also increase the intracellular calcium concentration, increase the intracellular reactive oxygen species, promote the expression of GRP78 and CHOP, lead to endoplasmic reticulum stress, and inhibit the expression of Kindlin-2 in cells to activate the inflammasome NLrp3, eventually leading to the apoptosis of NP cells. Compression force can inhibit PI3K/AKT/mTOR and JNK pathways, leading to NP autophagy, inhibit the expression of specific markers Brachyury and Glypican-3 in NP cells, promote P38-MAPK and RhoA/ROCK1 pathways leading to nucleus pulposus senescence, and accelerate extracellular matrix decomposition through the Hippo-YAP/TAZ pathway. Cyclic mechanical tension can directly lead to nucleus pulposus DNA damage, promote the expression of zinc ion channels, increase intracellular MMP, activate the P53-p21-Rb pathway, and lead to extracellular matrix degradation.

MMPs). ZIP8 mediates zinc ion transport, which is essential for MMP activity, and together they promote ECM degradation via NF-κB signaling [50], as shown in **Figure 2**.

Protective mechanisms of biomechanical factors on NP cells

Although biomechanical factors can contribute to the degeneration and apoptosis of NP cells through various mechanisms, multiple protective responses can counteract these deleterious effects.

Mechanical stress typically induces NP cell apoptosis and reduces ECM synthesis. However, mechanical growth factor (MGF) has been shown to reduce NP cell apoptosis, and exogenous MGF administration can reverse stress-induced apoptosis [51]. During excessive mechanical stretch, inhibition of the NF-κB pathway through downregulation of p65 expression can reduce inflammation, inhibit apoptosis, and mitigate NP cell degeneration [52].

Compressive stress decreases circRNA-CIDN expression, yet its overexpression inhibits NP cell apoptosis under such conditions [53]. Compression also upregulates TIGAR expression, which enhances NADPH production, thereby reducing both apoptosis and autophagy to preserve NP cell viability [54].

Tauroursodeoxycholic acid protects NP cells by counteracting apoptosis and inhibiting ERS [55]. Cyclosporine A alleviates compression-induced apoptosis in NP-derived mesenchymal stem cells (NP-MSCs) by attenuating mitochondrial dysfunction and oxidative stress [56].

Mechanically sensitive ion channel Piezo1 mediates calcium influx upon stress activation. shRNA-mediated knockdown of Piezo1 reduces intracellular calcium levels and stabilizes mito-

chondrial membrane potential, thus protecting NP cells [57]. Pioglitazone (PGZ) mitigates compression-induced oxidative stress and mitochondrial apoptosis in NP-MSCs, repairs ultrastructural damage, and downregulates apoptosis-related proteins such as cytochrome c and Bax [58].

Relationship between biomechanical forces and AF cells of the intervertebral disc

Injury mechanisms of biomechanical factors on AF cells

Mechanical tensile forces alter the structural integrity of AF cells, weakening the mechanical properties of the outer AF. Prolonged exposure can lead to the formation of microcracks that propagate radially from the NP to the outer annulus, disrupting fibrous integrity [59]. High cyclic stretch enhances p38 MAPK activity, activates the SMAD1/5/8 signaling pathway, and upregulates osteogenic markers such as Runx2 and osterix, promoting osteogenic differentiation and disc sclerosis [60].

Excessive mechanical loading also induces endoplasmic reticulum stress and ROS production, increasing the expression of inflammasome-related proteins such as NLRP3 and IL-1β in human AF cells, thereby accelerating degeneration [4]. Moreover, mechanical tension interacts with TNF-α, enhancing proinflammatory cytokine expression and causing cytoskeletal sclerosis, which increases AF cells' sensitivity to mechanical loading and exacerbates degeneration [61].

High mechanical strain suppresses cell proliferation and telomerase activity, reduces lectin and type I collagen expression, and increases senescence markers such as p16 and p53 [27]. It also promotes apoptosis, elevates caspase-3 and MMP3 activity, and impairs matrix synthesis in AF cells [62].

Protective mechanism of biomechanical factors on AF cells

Several mechanisms have been identified that protect AF cells from biomechanical stress-induced injury. As previously noted, mechanical stress induces inflammasome activation; however, metformin exerts anti-inflammatory effects by upregulating Col1, COX-2, and MMP-13, while reducing PGE2 production. Mechanical stretching enhances metformin's protective function under combined inflammatory and mechanical stimulation [63].

TRPV4 mediates inflammation under excessive cyclic tensile force, increasing IL-6, IL-8, and PGE2 release. Selective TRPV4 antagonists reduce IL-6/IL-8 secretion and inflammation in AF cells [64]. Moderate mechanical stress suppresses Cav1-mediated signaling, promotes ECM synthesis, restores NP hydration, and facilitates disc regeneration [65].

Physiological-range tensile force maintains proteoglycan synthesis and delays AF degradation [66]. Although cyclic stretch downregulates β1 integrin expression in rat AF cells, overexpression of β1 integrin mitigates stretch-induced apoptosis [67]. These protective substances and mechanisms are summarized in **Table 1**.

Relationship between biomechanics and the intervertebral disc endplate

Injury mechanisms of biomechanical stress on the endplate

Mechanical stress exerts complex effects on the endplate. Cyclic mechanical stretch activates NF-κB signaling, increasing MMP13 expression and promoting endplate cartilage degeneration [13]. Overexpression of TGF-β, triggered by mechanical stress, accelerates pathological calcification of the endplate, while TGF-β inhibition offers protective potential against intervertebral disc stenosis [5]. Mechanical traction disrupts nutrient transport from the endplate into the disc in the short term [7], and cyclic stretch induces cartilage endplate calcification via microRNA-mediated regulation in chondrocytes [68].

Protective mechanisms of biomechanical factors on the endplate

Although cyclic mechanical tension promotes endplate chondrocyte degeneration, the TGF-β/Smad2 signaling pathway counteracts this process by regulating the miR-455-5p/RUNX2 axis [69]. miR-365 normally promotes chondrocyte proliferation but is downregulated by mechanical stress. HDAC4 overexpression inhibits miR-365's protective role in endplate chondrocytes [70]. Increased osteoclast activity renders the

Table 1. The protective mechanisms of the different targets on cells

Target	Mechanism	Phenomenon
TIGAR	Promote NADPH production	Reduce NP cell apoptosis
TUDCA	Inhibit ERS	
HSP70	Inhibit mitochondrial division	
Resveratrol	Inhibit ERK1/2 pathway	
Ginsenoside Rg1	Inhibit AP1/TAZ signaling pathway-related protein expression	
CsA	Inhibit NP-MSCs mitochondrial dysfunction and oxidative stress	Protect NP-MSCs
PGZ	Reduce oxidative stress and mitochondrial apoptosis of NP-MSCs	
PUR	Activate PI3K/Akt pathway	Inhibit apoptosis of NP-MSCs
ShRNA-Piezol	and mitochondrial membrane potential	Protect NP cells
SIRT1	Inhibit NF-κB pathway	
RBMS3	Inhibit Wnt/nt/bit Wnt/ellsl	
RhTSG-6	Block IL-1β-induced p38	
Mangiferin	Inhibit NF-κB pathway	
Resveratrol	Activate PI3K/Akt pathway	Promote the synthesis of extracellular matrix
OP-1	Inhibit p38MAPK pathway	
Resveratrol	Regulate ROS/NF-κB pathway	Slow down the senescence of NP cells
Recombinant human Apclin-13	Activate PI3K/AKT pathway	Protect AF cells
Metformin	Reduce the inflammatory response of AF cells	Protect AF cells
Selective TRPV4 antagonists	Reduce the release of IL6 and IL-8	Reduce the inflammatory response of AF

TUDCA: Tauroursodeoxycholic acid, CsA: Cyclosporine A.

endplate porous and destabilizes the disc. Panax notoginseng saponins, a traditional Chinese medicine, exhibits anti-osteoclast activity [71].

Challenges and future directions in biomechanical research on IDD

Biomechanical forces are key contributors to lumbar disc degeneration. However, how the mechano-chemical coupling mechanisms alter the internal stress distribution, by which specific loading types affect MMP expression, ECM metabolism, and other biochemical pathways, remain poorly understood.

Despite recent advances, the complex anatomical and material properties of the lumbar spine hinder comprehensive understanding of disc biomechanics under different loading scenarios (e.g., compression, flexion-extension, torsion, and combined motions). Current mathematical and material models remain limited in simulating the true biomechanical states of lumbar discs during degeneration.

Future research should focus on micromechanical alterations within disc components under various loading conditions and further elucidate the biomechanical properties of degenerative discs. Building accurate 3D finite element models will be crucial for simulating the mechanical environment of disc degeneration and translating biomechanical insights into clinical strategies.

Conclusions

This review demonstrates the intricate and inseparable relationship between biomechanics and intervertebral disc health. Different types, magnitudes, and durations of mechanical loading exert both beneficial and detrimental effects on disc tissues. Appropriate loading conditions can stimulate protective signaling pathways, enhance ECM synthesis, and inhibit harmful molecular processes in the NP, AF, and endplates.

However, once the mechanical load exceeds a physiological threshold in intensity or duration, it can trigger mitochondrial apoptosis, ERS, autophagy, and ultimately cell death. Therefore, interventions such as neck, shoulder, back exercises and even manual therapy, may

reduce oxidative stress and delay disc degeneration through specific signaling pathways.

In clinical settings, low back pain is a common manifestation of IDD, and mechanical loading plays a direct role. Mechanical stress can lower disc pH via cytokine and inflammatory activation, triggering nerve stimulation and pain. Thus, this review not only elucidates the biomechanical mechanisms behind low back pain but also proposes new directions for future research.

In summary, biomechanical factors act as a double-edged sword in regulating disc physiology. This review first summarizes the macro-level injury and protection mechanisms of biomechanics and then analyzes their micro-level effects on NP, AF, and endplate cells. Based on this framework, numerous newly discovered pathways and substances over the past five years are highlighted to identify future therapeutic breakthroughs.

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Disclosure of conflict of interest

None.

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