Review

Current Mechanobiological Pathways and Therapies Driving Spinal Health

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Current Mechanobiological Pathways and Therapies Driving Spinal Health

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Abstract: Spinal health depends on the dynamic interplay between mechanical forces, biochemical signaling, and cellular behavior. In this review, we explore how key molecular pathways, including integrin, YAP and TAZ, Piezo, and Wnt with beta-catenin, actively shape the structural and functional integrity of spinal tissues. These signaling mechanisms respond to physical cues and interact with inflammatory mediators such as interleukin-1 beta, interleukin-6, and tumor necrosis factor alpha, driving changes that lead to disc degeneration, vertebral fractures, spinal cord injury, and ligament failure. New research is emerging that shows scaffold-designs that can directly harness these pathways. Further, new stem cell-based therapies have been shown to promote disc regeneration through targeted differentiation and paracrine signaling. Interestingly, many novel bone and ligament scaffolds are modulating anti-inflammatory signals to enhance tissue repair and integration, as well as prevent scaffold degradation. Neural scaffolds are also arising. These mimic spinal biomechanics and activate Piezo signaling to guide axonal growth and restore motor function. Scientists have begun combining these biological platforms with brain-computer interface technology to restore movement and sensory feedback in patients with severe spinal damage. Although this technology is not fully clinically ready, this field is advancing rapidly. As implantable technology can now mimic physiological processes, molecular signaling, biomechanical design, and neurotechnology opens new possibilities for restoring spinal function and improving the quality of life for individuals with spinal disorders.

Keywords: spinal regeneration; mechanobiology; tissue engineering; neural scaffolds; bone repair; stem cell therapy; intervertebral disc degeneration; inflammation modulation; bioactive biomaterials; regenerative medicine

Introduction

The human spine is the central pillar of structural support, mobility, and neural protection. Its health hinges on intricate molecular signaling pathways that orchestrate cellular responses to mechanical forces, inflammation, and tissue remodeling. These pathways are deeply rooted in immune modulation, cascade regulation, molecular machinery, and degenerative factors like osteoarthritis, disc degeneration, and spinal cord injuries. As such, in this review we synthesize the biochemical pathways behind the fundamental mechanobiology of the spine. Additionally, we explore new computational approaches that are helping the physical structure of the spine, as well as helping clinicians and researchers understand what health factors go into spine maintenance and

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regeneration. Our goal in doing so is to provide an updated review that also demonstrates how emerging technology and techniques are changing the landscape of spine health research.

1. Mechanotransduction in Spinal Tissues

Mechanotransduction is a process where cells convert mechanical stimuli into biochemical signals to respond or initiate movement [1]. The spine's intervertebral discs, vertebrae, ligaments, and cord constantly experience this mechanical loading from posture, movement, and weight-bearing. Even without movement, weight-bearing alone triggers molecular pathways that regulate cellular behavior, extracellular matrix (ECM) maintenance, and inflammatory responses [1,2]. Thus, understanding mechanotransduction in the spine is critical for developing tissue-engineered solutions for conditions where mechanical imbalances disrupt signaling homeostasis, namely degenerative disc disease and osteoarthritis.

1.1. Integrin-Mediated Signaling in Intervertebral Discs

Intervertebral discs (IVDs) cushion the spine and absorb compressive forces during movement [3]. Integrins, transmembrane receptors, mediate mechanotransduction by linking the ECM to the cytoskeleton [4]. In the nucleus pulposus, integrins such as $\alpha 5\beta 1$ bind to fibronectin and transmit mechanical signals that activate focal adhesion kinase (FAK) [5]. FAK will then phosphorylate downstream targets, initiating pathways like ERK/MAPK, which regulate gene expression for ECM components such as collagen II and aggrecan [6]. These molecules will then maintain disc hydration and fundamental resilience in order to absorb shock from weight bearing. Normally, this repetitive process ensures that movements can be quick and painless. If patients excessively weight-bear or the ECM degrades, this will largely dysregulate the integrin signaling process. In turn, production of a proteoglycan called aggrecan that makes up the cartilage structure will drop, and this will accelerate disc degeneration [7]. Integrin signaling can be quite dynamic, with the best example being in the disc's response to cyclic loading. Moderate mechanical stress enhances integrin activation and promotes anabolic gene expression [8]. However, prolonged or excessive compression disrupts integrin-ECM interactions, triggering catabolic pathways [9]. For instance, high loads increase matrix metalloproteinase (MMP) expression, which are zinc-binding proteolytic enzymes that can remodel the ECM, and this in turn degrades collagen and proteoglycans [8,9]. This imbalance ultimately leads to disc herniation. Emerging engineering strategies like scaffolds with tunable stiffness are especially beneficial here because they can match the stiffness of surrounding tissue. Specifically, these scaffolds optimize osteointegration by enhancing osteoblast mechanosensitivity within a narrow stiffness window (~0.7–3 MPa), promoting maximal f-actin polymerization and mineral deposition at the bone-implant interface, thereby reducing stress shielding and improving long-term implant fixation [10–12].

Integrin signaling also intersects with inflammatory pathways in the IVD [13]. Mechanical overload induces cytokine release, such as IL-6 (a key inflammatory mediator), which amplifies MMP activity. IL-6 then binds to its receptor, activating JAK/STAT signaling [14,15]. This then upregulates catabolic genes. This feedback loop is what exacerbates disc degeneration. The clinical relevance of integrin signaling extends to regenerative medicine as well. Stem cell therapies for IVD repair rely on mechanotransductive cues to direct differentiation. Mesenchymal stem cells (MSCs) cultured on stiff scaffolds upregulate integrin expression [16], enhancing chondrogenic differentiation [17]. This process mirrors native disc cell behavior, where mechanical cues drive ECM synthesis [1–3]. However, translating these findings to clinical practice requires scaffolds that replicate the disc's viscoelastic properties so that integrins are not over-activated. Excessively stiff substrates risk inducing aberrant mechanotransduction, leading to cytoskeletal hyperactivation and premature matrix degradation via upregulated catabolic signaling. Additionally, many current scaffold systems lack the microelastic gradients required to guide region-specific differentiation in the IVD niche [18]. Novel biomaterials like water-annealed glutenin-chitosan composites show promise in addressing

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this limitation by offering tunable stiffness and microarchitectural control [19], yet their translation to orthopedic applications remains underexplored.

1.2. YAP/TAZ Pathway in Vertebral Bone Mechanobiology

Vertebral bones withstand extensive compressive and tensile forces to maintain spinal stability. The YAP/TAZ pathway is a mechanosensitive transcriptional regulator that governs osteoblast activity in response to these forces [20]. Mechanical loading activates YAP/TAZ by inhibiting their phosphorylation, which facilitates nuclear translocation. In the nucleus, YAP/TAZ bind TEAD transcription factors and upregulate osteogenesis promoiting genes like RUNX2 [21,22]. Normally, this cycle will balance bone remodeling with mechanical demands. Thus, YAP/TAZ is very important for maintaining the vertebrae.

Osteoporosis can arise because significantly reduced mechanical loading (e.g., through a lack of mobility or inactive lifestyle) enhances YAP/TAZ phosphorylation [20–22]. This makes sense as phosphorylation would inactive a less frequently used mechanism and sequester it in the cytoplasm. In turn, osteoblasts can not differentiate and bone loss begins. Unfortunately, this may be a reinforcing cycle as vertebral fractures can become more common and hinder mobility even further. YAP/TAZ also modulates inflammatory responses in the vertebral bone. Mechanical stress induces IL-1β release, which suppresses YAP/TAZ activity through NF-κB signaling. This inflammatory cascade reduces osteoblast viability and accelerates bone resorption [23]. Osteoarthritic patients often experience sclerosis in their vertebral endplates because of IL-1β-driven inflammation exacerbating YAP/TAZ dysregulation. This interplay between YAP/TAZ and mechanotransduction can inform new regenerative strategies. For example, in tendon fibroblasts, 4% uniaxial stretching at 0.5 Hz attenuated IL-1β-induced COX-2 and MMP-1 expression and reduced PGE2 secretion [24], highlighting the anti-inflammatory potential of sub-physiological strain. Analogously, graded spinal loading in osteoporotic patients may downregulate NF-κB-mediated YAP/TAZ suppression, promoting osteoblast viability while curbing catabolic remodeling [25]. These findings support the development of biomechanically tuned rehab regimens and viscoelastic scaffolds engineered to deliver anti-inflammatory mechanotransductive cues within the degenerating vertebral niche.

1.3. Piezo Channels in Neural Mechanosensing

The spinal cord relies on mechanosensitive ion channels like Piezo1 and Piezo2 to detect stimuli [26]. Piezo channels are specifically activated by membrane tension and regulate calcium influx in neurons and glia. In the spinal cord, Piezo2 in sensory neurons mediates proprioception. Dysfunctional Piezo signaling therefore disrupts core spinal function [27]. In spinal cord injuries (SCIs), mechanical trauma damages neurons, impairing Piezo2. This disrupts proprioceptive feedback and induces motor deficits. On the other hand, Piezo1 is expressed in astrocytes and modulates inflammatory responses post-injury [28]. Excessive mechanical stress activates Piezo1, then releasing IL-6 and TNF-α, which drive up neuroinflammation [29]. Piezo channels also influence spinal cord regeneration. Many theoretical and animal models have also emerged around how Piezo signaling can be manipulated for regeneration. In zebrafish, Piezo1 activation enhances axonal growth, suggesting a conserved role in neural repair [30]. In humans, however, regenerative capacity is limited, partly due to inhibitory ECM components. Recent findings reveal that LOX-driven ECM remodeling upregulates neuronal Piezo1 expression, intensifying calcium influx and ferroptosis in injury models [31]. Inhibition of Piezo1 with agents like GsMTx4 not only attenuates neuronal damage but also restores cognitive function in hypoxia-induced brain injury [15,32]. These data suggest that mechanotransductive crosstalk between ECM stiffness and Piezo1 activation represents a modifiable axis for promoting spinal cord regeneration and mitigating neuroinflammation post-SCI.

Piezo channel regulation may also help with chronic pain management. Aberrant Piezo2 activation in dorsal root ganglia contributes to mechanical allodynia [33]. Recent preclinical models demonstrate that targeted depletion or chemogenetic silencing of Piezo2-expressing nociceptors

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effectively blocks mechanical allodynia and weight-bearing pain without exacerbating joint degeneration [34–37]. Co-expression of Piezo2 and TrkA in human DRGs underscores a conserved NGF-Piezo2 signaling axis implicated in chronic osteoarthritis pain [38]. These findings have catalyzed new developments of intra-articular Piezo2 inhibitors and DREADD-based neuromodulation strategies as next-generation, proprioception-sparing analgesics.

1.4. Wnt/β-Catenin Signaling in Ligament Mechanobiology

Spinal ligaments like the ligamentum flavum stabilize the spine under tensile forces. Wnt/β-catenin signaling is a mechanosensitive pathway that regulates ligament fibroblast activity by activating Wnt ligands, which bind Frizzled receptors and stabilize β-catenin [39]. Nuclear β-catenin upregulates genes like COL1A1, encoding collagen I, and ultimately strengthens the ligament [40]. This pathway maintains ligament elasticity, preventing hypermobility and spinal instability. In healthy spines, Wnt/β-catenin balances ECM synthesis with degradation, supporting dynamic movement [41–43]. Constant loading disrupts Wnt/β-catenin signaling, compromising ligament function [44]. In hypertrophic ligamentum flavum, excessive tensile stress overactivates β-catenin, increasing collagen deposition and fibrosis. This stwiffens ligaments, contributing to spinal stenosis [45]. Pharmacological Wnt inhibitors, such as sclerostin, could mitigate fibrosis, restoring ligament flexibility [46]. New tissue-engineered ligaments are beginning to arise that can deliver controlled mechanical stimuli, which would normalize Wnt/β-catenin activity and hypertrophy [47–49]. Inflammatory mediators modulate Wnt/β-catenin signaling in ligaments. IL-6, induced by mechanical overload, suppresses Wnt activity via SOCS3, reducing collagen synthesis [50]. This imbalance weakens ligaments, increasing injury risk.

Fortunately, Wnt/β-catenin signaling informs regenerative approaches for ligament injuries. MSCs cultured under tensile strain upregulate β-catenin and have been shown to enhance tenogenic differentiation [51–53]. Scaffolds that replicate ligament mechanics could direct MSC fate, producing functional tissue replacements [54]. Emerging scaffold designs now leverage biomechanical stimuli to spatially modulate Wnt/β-catenin gradients and tenogenic gene expression in situ [55]. Recent ligament-on-a-chip platforms and high-fidelity microphysiological systems (MPS) incorporating tensile loading have validated β-catenin-mediated tenogenesis in human MSCs under physiomimetic strain [51,56–58]. These models are accelerating the translation of mechanoresponsive, stem cell-laden scaffolds for enthesis repair and next-generation ligament reconstruction.

2. Inflammatory Signaling in Spinal Health

Inflammation can both mediate repair and exacerbate degeneration. Inflammatory signaling is driven by cytokines like IL-6, TNF-α, and IL-1β in response to mechanical stress, injury, and infection [1,2,14,17,24]. Dysregulated inflammation can also be linked to many spinal disorders, and can even be improperly suppressed through post-operative medication.

2.1. IL-6/JAK/STAT Pathway in Disc Degeneration

As we mentioned previously, IL-6 is a pleiotropic cytokine that drives inflammatory responses in IVDs. Mechanical overload or injury triggers IL-6 release from nucleus pulposus cells and the JAK/STAT pathway activates [13–15]. IL-6 binds its receptor, recruiting JAK kinases that then phosphorylate STAT3. Nuclear STAT3 upregulates MMPs and ADAMTS enzymes, degrading ECM components like aggrecan [59,60]. This catabolic cascade reduces disc height and causes pain. Chronic IL-6 signaling perpetuates inflammation in the IVD. STAT3 also induces IL-6 expression, creating a positive feedback loop [61]. This amplifies neuroinflammation, sensitizing nociceptors and contributing to chronic back pain. However, anti-IL-6 treatments like tocilizumab interrupt this cycle and reduce MMP activity and pain [62]. Additionally, newly studied IVD scaffolds integrate high-molecular-weight hyaluronic acid (HMWHA) and genipin-crosslinked fibrin to suppress IL-6 and TNF-α signaling via CD44 and NF-κB inhibition, respectively, while preserving ECM architecture

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[63]. Injectable hydrogels loaded with lactate oxidase-catalase fusion enzymes additionally have been shown to modulate acidic, ROS-rich NP microenvironments, reversing immune cell recruitment and IL-6 amplification [64–66]. Ideally, this can be apart of post-operative recovery and prevent over-inflammation through the JAK/STAT pathway. Next-generation nanoparticle-based delivery platforms including PLGA or PCL nanocarriers encapsulating anti-IL-6 siRNA or IL-1ra peptides can also sustain release kinetics and target cytokine blockade in avascular disc tissue [67], which can be helpful in rehabilitation.

2.2. TNF-α/NF-κB Pathway in Osteoarthritis

TNF-α is another pro-inflammatory cytokine that is connected to osteoarthritis [68]. Mechanical stress or injury induces TNF-α release from chondrocytes, activating NF-κB. TNF-α then binds TNFR1, recruiting TRAF2, which activates IKK and phosphorylates IκB [69,70]. This releases NF-κB, which will translocate to the nucleus and upregulate MMPs and COX-2. These enzymes subsequently degrade cartilage and induce pain, contributing to osteoarthritis [71]. Excessive TNF-α signaling will significantly accelerate cartilage loss, and NF-κB also induces IL-1β which amplifies inflammation. This creates a catabolic environment and erodes endplates [72].

Anti-TNF-α therapies like adalimumab can reduce NF-κB activity and therein slow degradation [73]. However, new tissue-engineered cartilage seem promising. Bioengineered constructs that use ECM scaffolds and are derived from collagen, hyaluronic acid, or silk fibroin seem to be able to modulate multiple inflammatory signaling pathways [74–76]. This includes NF-κB, p38 MAPK, and JNK, and they subsequently reduce TNF-α-induced catabolic mediators including MMP-13, COX-2, and ADAMTS-5 [76]. These scaffolds are further enhanced through growth factor loading with TGF-β1, IGF-I, or FGF-2, which not only stimulate anabolic processes like type II collagen and aggrecan synthesis but also suppress IL-1β and TNF-α-driven transcriptional programs by downregulating IKKβ phosphorylation and restoring IκBα stability [77–80].

In parallel, preconditioning of mesenchymal stem cells (MSCs) with decellularized stem cell matrices (DSCMs) has been shown to be a useful immunomodulatory approach [81]. These DSCM-expanded MSCs show enhanced resilience against IL-1β- and TNF-α-induced inflammatory cues, with upregulation of antioxidant defenses and increased secretion of anti-inflammatory cytokines like IL-10 [81]. Mechanistically, DSCM preconditioning enhances MSC expression of chondrogenic transcription factors while simultaneously downregulating NF-κB nuclear translocation and pro-apoptotic gene expression [82]. Notably, intra-articular delivery of DSCM-preconditioned MSCs in large-animal models results in robust hyaline-like cartilage regeneration, reduced type I collagen deposition, and minimal macrophage infiltration [83].

2.3. IL-1β/MAPK Pathway in Spinal Cord Injury

IL-1β is another potent inflammatory cytokine that shapes the spinal cord's response to injury. Trauma induces IL-1β release from microglia, activating MAPK pathways (p38, JNK, ERK) [84,85]. IL-1β then binds IL-1R, recruiting MyD88, which activates TAK1. TAK1 will then phosphorylate MAPKs. Nuclear MAPKs upregulate pro-inflammatory genes, including IL-6 and TNF-α, therein exacerbating neuroinflammation [85,86]. This cascade impairs neuronal survival and contributes to many motor deficits in SCIs. Thus, chronic IL-1β signaling perpetuates neuroinflammation in SCI patients. MAPKs also induce iNOS, producing nitric oxide, which damages neurons. This creates a toxic microenvironment that further hinders regeneration [87]. Fortunately, new tools are being designed to directly attenuate TNF-α–driven inflammatory cascades and catabolic matrix remodeling. ECM-mimetic scaffolds constructed from high-density type II collagen, gelatin-methacrylate (GelMA), or hyaluronic acid-based hydrogels have been functionalized with anti-inflammatory agents such as TGF-β3, IL-10, or FGF-18, enabling localized inhibition of the NF-κB and MAPK pathways in chondrocytes and synovial fibroblasts [88,89]. These scaffolds suppress the expression of downstream targets including MMP-13, ADAMTS-5, iNOS, and COX-2 by interfering with TNF receptor-associated factor (TRAF) signaling and stabilizing cytoplasmic IκBα, thus

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preventing nuclear translocation of p65/p50 NF-κB dimers [88–90]. Some other strategies that we found in the literature are nanoparticle-based delivery systems (specifically, PLGA or mesoporous silica nanoparticles) to encapsulate small molecule IKKβ inhibitors or anti-TNF-α siRNA [90–93] and spatiotemporally release within the hypoxic cartilage environment.

Saparov et al. (2016) showed that preconditioning mesenchymal stem cells (MSCs) using hypoxic three-dimensional culture or inflammatory cytokines such as IL-1β and TNF-α enhances their immunomodulatory capacity [94]. These preconditioned MSCs increase anti-inflammatory mediator expression, specifically the IL-1 receptor antagonist prostaglandin E2 (PGE-2), as well as heme oxygenase-1 (HMOX1), while reducing activation of proinflammatory pathways including NF-κB and MAPK. They also exhibit greater resistance to apoptosis and upregulate survival genes such as BCL-2 and AKT. In addition, they promote chondrogenic activity by increasing expression of SOX9 and aggrecan. In animal models of inflammatory arthritis, intra-articular injection of these MSCs significantly reduces synovial thickening, subchondral erosion, and local TNF-α levels, while restoring cartilage with hyaline-like features and improved biomechanical strength [94].Thus, Saparov et al. suggest that by attenuating these inflammatory cascades, MSCs may preserve extracellular matrix integrity, suppress catabolic signaling, and support functional recovery in damaged tissue.

2.4. Chemokine Signaling in Ligament Inflammation

Chemokines such as CCL2 and CXCL8 also regulate inflammatory responses in spinal ligaments [95]. Mechanical strain or injury induces chemokine release from fibroblasts, activating G-protein-coupled receptors (GPCRs). CCL2 binds CCR2, recruiting monocytes, which release IL-6 and TNF-α [96,97]. This amplifies inflammation, contributing to ligament hypertrophy and spinal stenosis. CXCL8, by activating CXCR1/2, enhances neutrophil infiltration, exacerbating tissue damage [97]. Chronic chemokine signaling will therefore perpetuate ligament inflammation. CCR2 activation induces NF-κB, upregulating MMPs, which degrade collagen. This weakens ligaments and increases injury risk. While anti-CCL2 antibodies could reduce monocyte recruitment [98], emerging research is also showing that it can be beneficial to directly target TNF-α and NF-κB signaling at the cellular and molecular levels. DSCM expands MSCs with enhanced resistance to IL-1β and TNF-α, maintaining viability and suppressing inflammatory cascades through reduced NF-κB nuclear translocation [99]. These MSCs show increased expression of IL-1Ra, HMOX1, and SOD2, and decreased TNFR1 and pro-apoptotic genes, enhancing chondrogenic potential [99–101]. Intra-articular delivery of DSCM-expanded MSCs in TNF-α-induced arthritis models reduces synovial thickness, inflammatory cytokines, and ECM degradation [102]. Additionally, nanocarriers incorporating anti-TNF-α siRNA or small-molecule IKKβ inhibitors have proven that they can maintain efficacy in hypoxic, acidic environments [103]. These systems block TRAF6-IKKβ-IκBα signaling, reduce MMP13 and ADAMTS5 expression, and restore anabolic markers like ACAN and COL2A1. Together, these approaches offer multi-tiered suppression of catabolic signaling, promote immune homeostasis, and support durable cartilage regeneration.

It is also important to note that chemokines intersect with mechanotransduction in ligaments [104]. Tensile strain activates integrins, therein enhancing CCL2 production via FAK. This proto-inflammatory pathway then amplifies GPCR signaling [105]. Biomaterials that mimic physiological tension could theoretically normalize integrin activation and reduce chemokine levels. Clinically, chemokine signaling is also a significant biomarker [106–108], such as how elevated CCL2 can correlate with stenosis symptom severity.

3. ECM Remodeling and Spinal Stability

The ECM must constantly modulate between synthesis and degradation. Molecular signaling pathways, including TGF-β, MMPs, and TIMPs, regulate ECM remodeling in spinal tissues [109]. These pathways respond to mechanical cues and inflammation, gradually shaping tissue architecture. When ECM remodeling goes wrong, many disorders including ligament fibrosis, disc

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degeneration, and osteoarthritis can arise. Understanding these pathways is therefore essential for developing tissue-engineered solutions for affected patients.

3.1. TGF-β/Smad Pathway in Disc ECM Synthesis

TGF-β is a growth factor that drives ECM synthesis in IVDs. When the spine is stimulated, TGF-β release from nucleus pulposus cells and will activate Smad signaling. TGF-β binds to its receptor, phosphorylating Smad2/3, which complexes with Smad4 and translocates to the nucleus. Smad2 upregulates genes like ACAN and COL2A1, encoding aggrecan and collagen II, respectively [110]. These proteins are overall responsible for maintaining disc hydration and resilience, supporting spinal mobility. In aged discs, reduced mechanical responsiveness decreases TGF-β expression, which means Smad activity is downregulated. This reduces aggrecan synthesis and compromises disc hydration. There are TGF-β agonists, including recombinant proteins, that could restore Smad signaling and help repair the ECM [111].

Recent work has identified DSCM as a potent immunomodulatory platform for expanding MSCs with enhanced resistance to TNF-α and IL-1β signaling. DSCM-expanded MSCs display reduced TNFR1 expression, decreased NF-κB nuclear translocation, and lower expression of pro-apoptotic genes, while upregulating IL-1Ra, HMOX1, and SOD2 [112,113]. These cells maintain chondrogenic gene expression, including SOX9 and COL2A1, even under inflammatory challenge. Intra-articular injection of DSCM-MSCs in TNF-α-induced arthritis models reduces synovial inflammation, suppresses expression of MMP13 and ADAMTS5, and preserves cartilage integrity [114,115]. Parallel studies have developed nanocarriers such as PLGA and mesoporous silica nanoparticles to deliver anti-TNF-α siRNA or IKKβ inhibitors directly to inflamed joints [116–118]. These systems inhibit TRAF6-mediated NF-κB activation, restore IκBα stability, and maintain anabolic signaling in chondrocytes. Collectively, these findings suggest that combining immunomodulatory MSCs with targeted cytokine interference offers a robust strategy to counteract TNF-α-driven joint degeneration and promote sustained tissue regeneration.

3.2. MMP-13/TNF-α Pathway in Vertebral Cartilage Degradation

MMP-13 is a collagenase that drives ECM degradation in vertebral endplates [119]. Mechanical stress induces TNF-α, which upregulates MMP-13 through NF-κB. TNF-α binds to TNFR1, activating IKK, which phosphorylates IκB and releases NF-κB. Nuclear NF-κB upregulates MMP-13 and collagen I and II are degraded. This erodes cartilage and thus drives osteoarthritis [120]. NF-κB also induces ADAMTS-5, and proteoglycan will be lost if this pathway is overactive [121]. This creates a catabolic microenvironment, causing endplate sclerosis and pain. MMP inhibitors, such as doxycycline, reduce ECM degradation and have been shown to effectively slow osteoarthritis progression [121]. Recent research demonstrates that Amygdalin (AMD), a bioactive cyanogenic glycoside, significantly attenuates NF-κB signaling by inhibiting p65 and IκBα phosphorylation in cartilage endplate chondrocytes [122]. In both in vivo LSI-induced IDD models and IL-1β-stimulated in vitro systems, AMD reduced MMP-13 and TNF-α expression while preserving type II collagen integrity [123]. This dual anti-catabolic and anti-inflammatory action restores endplate microarchitecture and disrupts the ECM-inflammation feedback loop. Such findings position AMD as a mechanistically targeted modulator of NF-κB signaling with translational potential for biotherapeutic intervention in discogenic osteoarthritis.

4. Regenerative Strategies for Spinal Health

Molecular signaling fundamentally drives stem cell differentiation, tissue repair, and successful biomaterial integration. Thus, researchers developing regenerative medicine strategies must account for mechanical, inflammatory, and epigenetic cues to ensure that regenerative interventions are not only biologically compatible but also functionally durable across diverse pathologies.

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4.1. Stem Cell Therapies for Disc Regeneration

Many new MSC therapy advancements are coming into mainstream research for intervertebral disc degeneration. Bone marrow-derived MSCs (BM-MSCs) and adipose-derived stem cells (ADSCs) are still the gold standard as cell sources due to their immunomodulatory profiles, hypoxia resilience, and nucleus pulposus-like differentiation [124,125].

Clarke et al. (2014) demonstrated that growth differentiation factor 6 (GDF6) promotes lineage-specific discogenic differentiation of BM-MSCs by upregulating NP markers (SOX9, KRT19, ACAN), enhancing the expression of ECM components including aggrecan and collagen II [126]. These findings suggest that GDF6-driven discogenic differentiation enhances ECM production and phenotype stability. MSCs can then be potentially better equiped or at the very least more resistant to this hostile environment. Similarly, Wei et al. (2014) reported that MSCs implanted into rabbit discs maintained long-term viability and synthesized key NP matrix proteins, leading to improved hydration and disc height [127]. These findings have catalyzed the use of GDF6, TGF-β3, and other morphogens in scaffold-based delivery platforms to promote phenotypic stability post-injection.

Hypoxic preconditioning is another emerging strategy to boost MSC resilience. Yang et al. (2022) showed that hypoxia-preconditioned MSCs had reduced apoptosis, increased collagen II deposition, and greater aggrecan retention in rat models of IDD [128]. These findings are consistent with other researchers who observed that low oxygen tension enhances NP-like gene expression in ADSCs through epigenetic reprogramming and HIF-1α stabilization [129,130]. Epigenetic modifiers like histone deacetylase inhibitors are also now being integrated into hydrogel systems to further modulate gene expression and differentiation trajectories [131].

Scaffold technologies have also evolved to accommodate the biomechanical demands of the IVD. Yang et al. (2024) demonstrated that viscoelastic sodium alginate-gelatine hydrogels, when seeded with BM-MSCs and subjected to dynamic compression, significantly enhanced TRPV4 activation and intracellular calcium influx, which in turn activated Wnt/β-catenin signaling and promoted osteogenic differentiation [132]. Additionally, composite scaffolds with fast stress relaxation properties facilitated MSC migration, improved adhesion, and upregulated key osteogenic markers such as RUNX2 and COL1A1 [132]. Dynamic bioreactor systems applying physiologic compressive strain (1.5%) were found to synergize with viscoelastic cues, maximizing osteogenesis through mechanical tuning of the TRPV4-Ca^{2+}-β-catenin axis.

Emerging studies have also begun experimenting with genetically engineered MSCs. Preclinical models are evaluating CRISPR-mediated silencing of senescence markers (e.g., p16INK4a) and overexpression of ECM-stabilizing proteins such as COMP and fibromodulin [133]. Additionally, extracellular vesicles (EVs) derived from MSCs - particularly exosomes carrying miR-140 and miR-21 - are being explored as cell-free alternatives that replicate paracrine therapeutic effects while minimizing over cell viability and tumorigenicity [134]. We strongly believe that future directions in this avenue include integrating MSCs into 3D-printed disc-like constructs, applying matrix-mimetic cues for zonal control of differentiation, and using ex vivo organ culture systems for high-throughput testing.

4.2. Bone Tissue Engineering for Vertebral Fractures

Currently, orthopedic surgeons will insert autologous bone grafts to treat complex bone defects. This involves harvesting bone from the patient's own body (e.g., the iliac crest) and transplanting it to the fracture site [135,136]. However, many patients may not be able to withstand this harvest. Fortunately, tissue-engineered bone constructs are emerging as a potential solution for fracture fixation. Mechanical loading of osteoblast-seeded scaffolds activates nuclear translocation of YAP and TAZ, which in turn upregulate osteogenic transcription factors such as RUNX2 and SP7 that promote ECM deposition and mineralization [137]. Scaffolds engineered with high compressive strength and viscoelastic compliance mimic vertebral biomechanical properties to enable structural support and biological integration. In preclinical models, these constructs have successfully repaired vertebral defects, restored bone density, and improved load-bearing capacity.

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Despite this progress, inflammation is still a major impediment. Trauma-induced IL-1β signaling activates the NF-κB pathway, suppressing YAP and TAZ activity and impairing osteoblast viability and differentiation [137]. To counter this, patients should also simultaneously recieve anti-inflammatory agents like such as TNF-α inhibitors or IL-1 receptor antagonists in the scaffold matrix. Scaffolds functionalized with bioactive peptides also stabilize BMP signaling and improve osteoinductive potential, particularly in osteoporotic contexts where systemic inflammation and matrix fragility are common [138–140]. Recent studies provide additional insight into inflammatory modulation. Zeng et al. (2024) demonstrated that Amygdalin (AMD) inhibits NF-κB signaling by preventing IκBα and p65 phosphorylation, thereby reducing downstream expression of MMP-13 and ADAMTS-5 [122]. In rat LSI-induced disc degeneration models, AMD preserved type II collagen and proteoglycan content while reducing TNF-α and IL-6 secretion [122,141]. Epigenetic modulation complements these regenerative efforts. Mechanical loading reduces repressive histone marks (e.g., H3K27me3) while increasing permissive modifications (e.g., H3K9ac) at osteogenic gene promoters [142], thereby enhancing transcriptional output.

4.3. Neural Technology for Rehabilitation and Support

Recent breakthroughs in neuroengineering have also dramatically expanded the therapeutic landscape. As is the case with many CNS-related conditions, complementary treatments alongside primary treatment can help many patients improve their QOL. We specifically argue that brain-computer interfaces (BCIs) can help many patients who are in end-stage spinal degeneration or spinal disease [143]. BCIs like those developed by Neuralink utilize high-density microelectrode arrays with over 3,000 channels per implant to enable direct bidirectional communication with cortical networks. These implants decode motor intent and, when coupled with spinal stimulation systems, can restore volitional control of paralyzed limbs [144]. Neuralink recently raised $650 million in Series E funding to conduct further clinical trials [145]. As its competitors like Synchron, Paradromics, Blackrock Neurotech, and Precision Neuroscience also develop their BCI or BCI-analogous technology, it seems that patients who have mobile difficulty or inability can soon benefit from new technology. In early human trials, Neuralink's "Telepathy" interface enabled a quadriplegic user to perform complex tasks using motor imagery [146], establishing a new benchmark in assistive neurotechnology. From a systems-level perspective, an ideal hybrid bioelectronic platform would blend Piezo-activated neural scaffolds with BCI-mediated feedback loops to foster real-time neuromotor control.

5. Conclusions

The mechanobiology of the spine reflects a complex interplay between molecular signaling, mechanical stress, inflammation, and tissue regeneration. As outlined in this review, core pathways such as integrin-FAK-MAPK, YAP and TAZ signaling, Wnt/β-catenin, and Piezo ion channels regulate spinal tissue homeostasis and respond to both biomechanical and inflammatory cues. These molecular systems govern structural integrity and functional responses in intervertebral discs, vertebrae, ligaments, and neural elements.

Recent advances in regenerative medicine have yielded promising therapeutic platforms. These include stem cell therapies tailored to disc microenvironments, tissue-engineered scaffolds that mimic native biomechanical properties, and neural interfaces that enable real-time feedback for spinal cord injury recovery. Each of these approaches leverages specific mechanobiological pathways to promote repair and restore function in damaged spinal tissues.

Despite these encouraging developments, several challenges remain. The translation of preclinical findings into clinical application requires careful attention to immune compatibility, long-term scaffold integration, and consistent signaling activation. Molecular targets such as IL-6, TNF-alpha, and IL-1 beta remain difficult to modulate without off-target effects, particularly within complex inflammatory environments. Neural interfaces and high-density electrode systems introduce additional concerns related to safety, durability, and ethical oversight.

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As research progresses, it is important to balance innovation with rigorous validation. Mechanobiology-informed therapies must be tested in scalable, reproducible systems that reflect the heterogeneity of spinal disorders. Technologies such as bioreactors, epigenetic modulation, and smart biomaterials offer new pathways to refine these interventions.

In conclusion, the integration of molecular insight with biomechanical innovation holds substantial promise for transforming spinal care. While caution is warranted due to the complexity of spinal biology, the careful development of mechanobiology-driven therapies has the potential to deliver personalized, effective, and long-lasting solutions for patients with spinal disease.

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