Mechanotransduction and its impact on regenerative medicine in orthopedic rehabilitation (Review)

BAOHUI WANG, XUEQIN ZENG, HUAJIAN LIU, LIANG LI, TAO LEI, YAFENG LI, QING FANG, YI CAO and BO DONG

Pain Ward, Department of Rehabilitation, Honghui Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi 710000, P.R. China

Received September 22, 2025; Accepted December 22, 2025

DOI: 10.3892/ijmm.2026.5798

Abstract. Mechanotransduction, the process by which cells convert mechanical stimuli into biochemical signals, serves as a fundamental biological mechanism driving tissue adaptation and repair in orthopedic rehabilitation. The present review explores how mechanical forces regulate cellular behavior in bone, cartilage, tendon and ligament healing, emphasizing their critical role in optimizing regenerative outcomes. Specialized mechanosensors, including integrins, ion channels and primary cilia, detect physical cues such as compression, tension and shear stress, activating downstream pathways that direct stem cell differentiation, matrix synthesis and tissue remodeling. The extracellular matrix functions not only as a structural scaffold but also as a dynamic mediator of mechanical signaling, influencing cellular responses to therapeutic loading. Clinically, mechanotherapy strategies, including controlled weight-bearing, eccentric exercises and devices providing dynamic compression, are designed to exploit these principles, promoting anabolic activity while preventing catabolic damage. Advances in biomechanically optimized scaffolds, bioreactor systems and technologies (such as low-intensity pulsed ultrasound) further demonstrate how targeted mechanical conditioning enhances tissue-engineered constructs and accelerates functional recovery. However, challenges remain in defining optimal loading parameters across diverse tissues and individual patients. Future directions should prioritize personalized rehabilitation protocols informed by real-time biomechanical monitoring and genetic profiling, alongside biomaterials that can adapt to *in vivo* mechanical cues. The integration of mechanobiology with regenerative medicine is paving the way for a new era in orthopedic rehabilitation. This evolution promises more precise, effective and biologically driven interventions that harness the innate mechanoresponsive capacity of the body to restore function.

Correspondence to: Dr Bo Dong, Pain Ward, Department of Rehabilitation, Honghui Hospital, Xi'an Jiaotong University, 555 Youyi East Road, Beilin, Xi'an, Shaanxi 710000, P.R. China
E-mail: dongbo8970@163.com

Key words: mechanotransduction, regenerative medicine, orthopedic rehabilitation, mechanosensors, cartilage regeneration, bone formation

Contents

1. Introduction

Orthopedic rehabilitation has long relied on mechanical interventions, such as physical therapy, exercise and load-bearing activities, to promote tissue repair and functional recovery (1,2). However, the biological mechanisms underlying these therapies have only recently been elucidated through advances in understanding mechanotransduction, the process by which cells convert mechanical stimuli into biochemical signals (3,4). This intricate interplay between physical forces and cellular responses plays a pivotal role in tissue regeneration, particularly in the bone, cartilage, tendons and ligaments (5,6). As regenerative medicine continues to evolve, understanding mechanotransduction offers new opportunities to enhance healing, optimize rehabilitation protocols and develop novel bioengineered therapies (7,8).

Mechanotransduction is a fundamental biological phenomenon that enables cells to sense and respond to mechanical cues such as tension, compression and shear stress (9,10). In orthopedic tissues, specialized cells including osteocytes, chondrocytes, tenocytes and mesenchymal stem cells (MSCs) possess mechanosensitive receptors (such as integrins, ion channels and primary cilia) that detect extracellular mechanical forces (11,12). These signals trigger intracellular cascades, such as the activation of Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ), Wnt/β-catenin and mitogen-activated protein kinase (MAPK) pathways, ultimately influencing gene expression, extracellular matrix (ECM) remodeling and tissue adaptation (13-15). The ECM itself acts as a dynamic scaffold that transmits and amplifies mechanical signals, further modulating cellular behavior (16,17).

Distraction histogenesis is the biological process that regenerates bone and soft tissue (18). In bone regeneration, mechanical loading stimulates the osteogenic differentiation of MSCs and osteoblasts while inhibiting osteoclast activity, thereby promoting bone formation and preventing resorption (19,20). Low-magnitude high-frequency vibration and controlled cyclic loading have shown promise in accelerating fracture healing and mitigating osteoporosis-related bone loss (21,22). Similarly, in cartilage repair, chondrocytes respond to dynamic compression by upregulating anabolic factors (such as aggrecan and collagen type II) while suppressing catabolic enzymes [such as matrix metalloproteinases (MMPs)] (23,24). However, excessive or aberrant loading can induce degenerative changes, highlighting the need for precise mechanotherapeutic strategies (25). Tendon and ligament healing, often hindered by poor vascularity and slow ECM turnover, also depends on mechanotransduction (26,27). Controlled mechanical stimulation enhances collagen alignment and tensile strength, whereas immobilization leads to tissue atrophy and fibrosis (28). Emerging evidence suggests that tendon stem/progenitor cells exhibit load-dependent differentiation, offering potential targets for regenerative interventions (29). The integration of mechanotransduction principles into regenerative medicine has led to innovative approaches in orthopedic rehabilitation (7,25).

Biomechanically optimized scaffolds, embedded with growth factors and designed to mimic native tissue mechanics, enhance stem cell recruitment and differentiation (30,31). Additionally, dynamic bioreactor systems apply physiologically relevant mechanical stimuli to engineered tissues, improving their functional maturation before implantation (32). Clinically, mechanotherapy, the therapeutic application of mechanical forces, has gained traction. Techniques such as extracorporeal shockwave therapy (ESWT) and pulsed electromagnetic fields (PEMFs) harness mechanotransduction to stimulate tissue repair, while personalized rehabilitation protocols leverage patient-specific loading regimens to maximize recovery (3,33). The optimal magnitude, frequency and duration of mechanical stimuli vary across tissues and individuals, necessitating further research into precision mechanotherapies. Additionally, the crosstalk between mechanical and biochemical signaling pathways must be deciphered to develop synergistic treatment strategies. Future advancements in biofabrication, smart biomaterials and artificial intelligence (AI)-driven biomechanical modeling hold promise for tailoring regenerative therapies to individual patient needs (34).

The present review comprehensively examines the fundamental mechanisms of mechanotransduction, detailing how specialized sensors convert physical forces into biochemical signals that direct cellular behavior. The present review explores the critical role of the ECM as a dynamic mediator of mechanical signaling and investigates tissue-specific responses in bone, cartilage, tendon and ligament regeneration. The discussion extends to the notable impact of mechanical loading on stem cell differentiation and the development of innovative biomechanical strategies in regenerative medicine, including advanced biomaterials and bioreactor systems. Clinically, the present review focuses on translating these principles into effective mechanotherapy protocols and personalized rehabilitation approaches. Finally, the prevailing challenges in defining optimal loading parameters are addressed and future directions are explored, emphasizing the potential of emerging technologies such as smart biomaterials and AI-driven modeling to create precise, biologically-driven interventions. By synthesizing these elements, the present review aims to highlight the transformative potential of integrating mechanobiology with regenerative medicine to advance orthopedic rehabilitation outcomes.

2. Cellular sensors and fundamental mechanisms of mechanotransduction

The conversion of mechanical forces into biochemical signals, a process fundamental to tissue repair, is initiated by specialized cellular structures known as mechanosensors. These sensors detect physical cues including compression, tension and fluid shear stress within the musculoskeletal environment (35). Principal among these are integrins, transmembrane receptors that form focal adhesion complexes, creating a critical link between the ECM and the intracellular cytoskeleton. These complexes act as primary force transduction hubs, sensing deformation and matrix stiffness. Additionally, stretch-activated ion channels (such as Piezo1) embedded in the cell membrane respond to mechanical perturbation by rapidly altering ion flux, particularly Ca^{2+}, to initiate immediate electrochemical signaling (36). On the surface of cells such as osteocytes and chondrocytes, primary cilia project as non-motile antennae, exquisitely tuned to sense subtle changes in fluid flow and pressure. Force detection by these sensors triggers a sophisticated cascade of intracellular signaling pathways. The mechanical signal is first propagated through the dynamic cytoskeleton, a network that distributes tension from the membrane to the nucleus (37). This mechanical energy is then converted into chemical signals through the activation of key mediators.

Mechanotransduction is the sophisticated process through which cells perceive external mechanical forces and convert them into intracellular biochemical responses (4,9). This fundamental mechanism is initiated by mechanosensors, which are specialized cellular structures that detect mechanical perturbations. Key sensors include integrins, which tether the intracellular cytoskeleton to the ECM, forming focal adhesion complexes that act as primary force transduction hubs (38,39). Additionally, stretch-activated ion channels (such as Piezo1) rapidly alter ion flux upon membrane deformation,

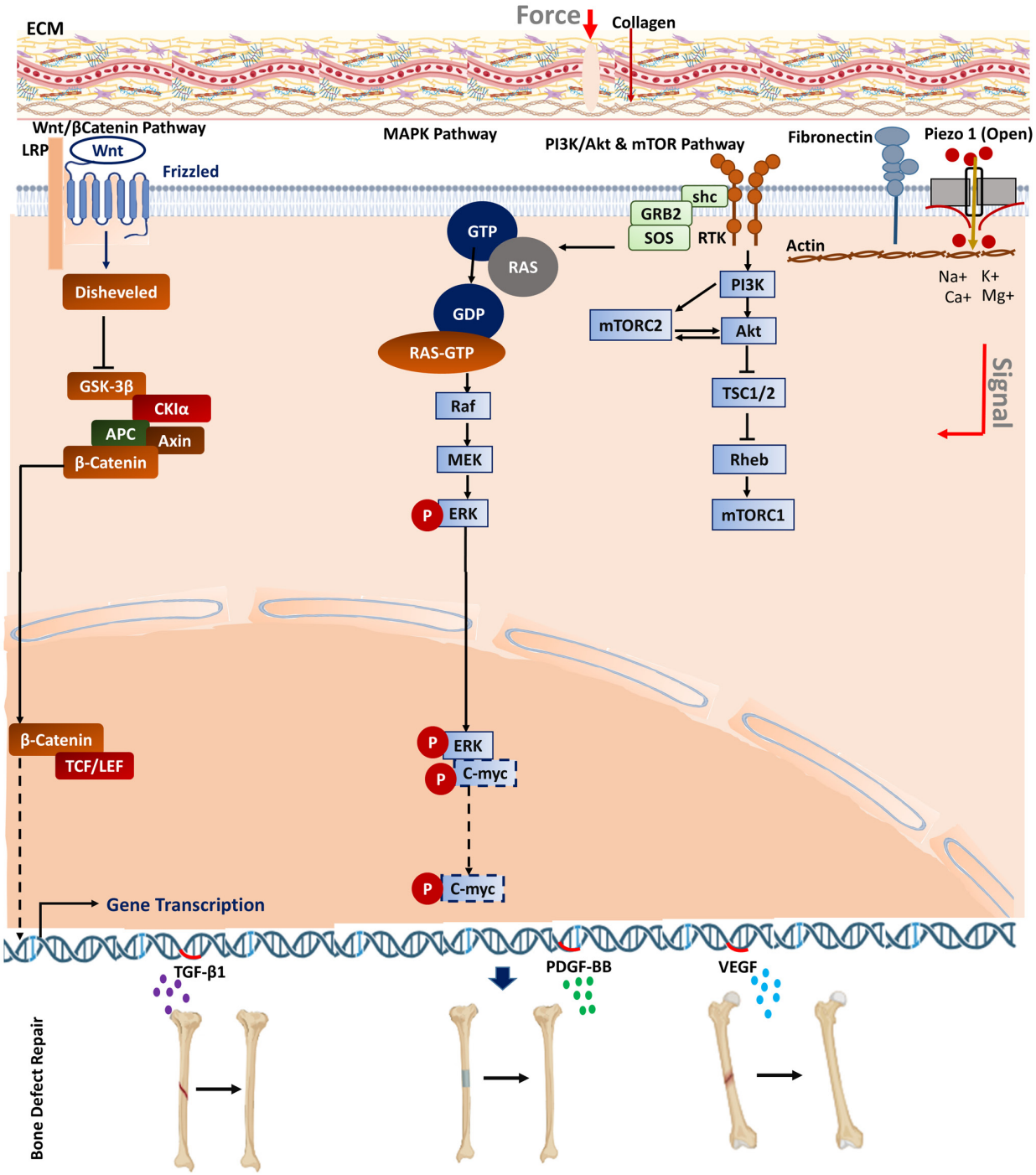

Figure 1. Mechanotransduction is fundamental to distraction histogenesis. Mechanotransduction begins when mechanical forces are applied to the ECM and cellular membranes, which in turn stimulate mechanosensitive ion channels, including Piezo1. The activation of these channels initiates downstream signaling cascades such as the Wnt/β-catenin, MAPK, PI3K/AKT and mTOR pathways that regulate critical cellular processes, including proliferation and differentiation. Concurrently, this mechanosensitive signaling stimulates the production of growth factors, namely TGF-β1, PDGF-BB and VEGF. These factors are then released into the circulation and transported to the injury site, where they promote bone lengthening and regeneration, in addition to supporting the repair and neogenesis of vascular and cutaneous tissues. ECM, extracellular matrix; LRP, lipoprotein receptor-related protein; GSK-3β, glycogen synthase kinase 3β; CKIα, casein kinase 1α; APC, adenomatous polyposis coli; TCF/LEF, T-cell factor and lymphoid enhancer-binding factor; RAS, rat sarcoma; Raf, rapidly accelerated fibrosarcoma; ERK, extracellular signal-regulated kinase; shc, SHC-adaptor protein; GRB2, growth factor receptor-bound protein; RTK, receptor tyrosine kinase; TSC1, tuberous sclerosis complex 1; Rheb, Ras homolog enriched in brain; PDGF-BB, platelet-derived growth factor-BB.

while primary cilia on chondrocytes and osteocytes function as cellular antennae, sensing fluid shear stress and compression (40). Force detection triggers a cascade of intracellular signaling pathways. The mechanical signal is propagated via the cytoskeleton, a dynamic network that distributes tension throughout the cell (37). This leads to the activation of key mediators such as the Hippo pathway effectors YAP and TAZ, which translocate to the nucleus to regulate genes responsible for proliferation and matrix synthesis (41,42). Fig. 1 depicts the key signaling cascades (such as the Wnt/β-catenin and MAPK pathways) activated by mechanosensitive ion channels, which further modulate cell fate decisions, including differentiation

Table I. Key cellular mechanosensors and signaling pathways.

Mechanosensor or pathway	Description	Function in mechanotransduction	(Refs.)
Integrins and focal adhesions	Transmembrane receptors that link the extracellular matrix to the intracellular cytoskeleton.	Form primary force transduction hubs; detect tension and stiffness (mechanoreciprocity) by sensing ECM deformation.	(38,48,49)
Stretch-activated ion channels (such as Piezo1)	Channels embedded in the cell membrane that open in response to membrane deformation.	Rapidly alter ion flux (such as Ca^{2+} influx) upon mechanical stress, initiating immediate signaling cascades.	(36)
Primary cilia	Non-motile, hair-like microtubule-based organelles projecting from the cell surface.	Act as cellular antennae sensing fluid shear stress, compression and osmotic pressure.	(50,51)
YAP/TAZ (Hippo pathway)	Transcriptional coactivators that shuttle between the cytoplasm and nucleus.	Act as central mediators; translocate to the nucleus upon mechanical stimulation to regulate genes for proliferation and matrix synthesis.	(14,52)
Wnt/β-catenin pathway	A highly conserved signaling pathway crucial for development and homeostasis.	Activated by mechanical loading (such as in bone, via sclerostin inhibition) to promote osteogenic differentiation.	(53,54)
Cytoskeleton	A dynamic network of actin filaments, microtubules and intermediate filaments.	Distributes and transmits tension throughout the cell, from the membrane to the nucleus.	(55,56)

and apoptosis (43,44). Crucially, mechanotransduction is bidirectional. Cells not only respond to forces but also actively exert contractile forces on their surroundings through actomyosin activity, a concept known as mechanoreciprocity (45,46). This continuous dialogue between cells and their biomechanical environment is essential for maintaining tissue homeostasis and is a critical target for guiding regenerative outcomes in orthopedic tissues (47). Key cellular mechanosensors and signaling pathways are shown in Table I (48-56).

3. Role of the extracellular matrix in mechanical sensing

The ECM is far more than a passive structural scaffold; it is a dynamic and active mediator essential for cellular mechanical sensing. The composition, architecture and physical properties of the ECM fundamentally govern how mechanical forces are transmitted, attenuated or amplified before reaching cellular mechanosensors (57). The stiffness of the ECM, or elastic modulus, provides a critical physical cue that directly influences cell fate. For instance, MSCs can sense this rigidity through integrin-mediated adhesions, a process known as durotaxis, which directs them toward osteogenic differentiation on stiffer, bone-mimetic substrates or adipogenesis on softer substrates (58). Beyond static properties, the viscoelasticity of the ECM, its ability to exhibit both elastic solid and viscous fluid behaviors, allows it to absorb and distribute energy from dynamic loading (59). This time-dependent response protects cells from sudden, damaging impacts while facilitating the transfer of beneficial, rhythmic strains. Furthermore, the molecular organization of the ECM is pivotal. The specific arrangement of fibrillar collagens, proteoglycans and glycoproteins creates a unique architectural landscape that filters mechanical signals (60). This organized network ensures that forces such as tension or compression are not merely felt as blunt pressure but are translated into specific, spatially guided biochemical instructions.

Crucially, the matrix acts as a biochemical reservoir that works in concert with mechanical inputs. Embedded growth factors and bioactive peptides are often sequestered within the ECM and can be released or activated in response to mechanical deformation (61). The mechanosensitive signaling triggers the production of growth factors including TGF-β1, platelet-derived growth factor-BB and VEGF, which are released into the circulation and transported to the injury site to promote bone lengthening and regeneration (62). This process, termed mechano-chemo transduction, creates a synergistic effect where physical forces directly modulate the local biochemical microenvironment. For example, mechanical strain can liberate TGF-β from its latent binding proteins in the matrix, thereby simultaneously providing a mechanical and a chemical stimulus for tissue repair (63). Therefore, the ECM is an indispensable partner in mechanotransduction; it functions as a sophisticated signal processor that contextualizes external mechanical loads, ensuring that the subsequent intracellular signaling cascades and transcriptional responses are appropriate for maintaining tissue homeostasis or initiating regeneration (60). This central role makes the rational design of ECM-mimetic biomaterials a paramount strategy in regenerative orthopedics.

4. Mechanotransduction in bone and cartilage regeneration

The regenerative processes in bone and cartilage are guided by mechanotransduction, although the specific cellular responses

differ due to the distinct physiological demands of each tissue (64-66). In bone regeneration, mechanical loading is a potent anabolic stimulus (67). Osteocytes, embedded within the mineralized matrix, act as the primary mechanosensors, detecting interstitial fluid flow shear stress generated during loading (68,69). This detection inhibits sclerostin expression, thereby unleashing the Wnt/β-catenin signaling pathway. This cascade promotes osteoblastic bone formation and suppresses osteoclastic resorption, making targeted mechanical stimulation a critical therapeutic strategy for enhancing fracture healing and combating osteoporosis (53,70,71). By contrast, cartilage regeneration presents a more complex mechanobiological challenge due to its avascular nature and low cellularity (72). Chondrocytes within the proteoglycan-rich ECM respond optimally to dynamic compression and hydrostatic pressure, which upregulate anabolic genes for type II collagen and aggrecan (73,74). However, the response is dependent on the nature, magnitude and frequency of the load. While physiological, dynamic loading promotes matrix synthesis and the chondrogenesis of MSCs, aberrant loading such as high-impact shear or prolonged static compression induces a catabolic state characterized by the release of inflammatory cytokines and matrix-degrading enzymes such as MMP-13, accelerating degeneration (74). This nuanced understanding is directly applied in rehabilitative medicine. For bone, low-magnitude high-frequency vibration and controlled weight-bearing protocols are used to stimulate healing (75). For cartilage, motion therapies and continuous passive motion devices are designed to provide beneficial dynamic compression while avoiding detrimental shear forces, thereby creating a pro-regenerative mechanical microenvironment (76).

5. Osteogenic responses to mechanical stimuli

Mechanical loading is a fundamental regulator of bone mass and architecture, with osteogenic responses following a well-established principle whereby bone forms in areas of high stress and resorbs in areas of disuse (77,78). This adaptive process, governed by mechanotransduction, is crucial for fracture healing and preventing osteoporosis (79). Osteocytes, comprising >90% of bone cells and entombed within lacunae, act as the orchestrators of this response; they detect minute deformations of the bone matrix, which cause interstitial fluid to flow within the canalicular network, generating shear stress across their extensive dendritic processes (69,80). This mechanical stimulation triggers a rapid biochemical response. Osteocytes downregulate the secretion of sclerostin, a key inhibitor of the Wnt/β-catenin signaling pathway (81,82). The subsequent activation of Wnt signaling in pre-osteoblasts and lining cells promotes their proliferation, differentiation and ultimately, bone formation (83). Concurrently, mechanical signals suppress osteocyte-supported receptor activator of nuclear factor κ-B ligand expression, thereby inhibiting osteoclastogenesis and bone resorption (84). Mechanical stimulation directs MSCs toward becoming bone-forming osteoblasts. This occurs by activating osteogenic transcription factors [such as β-catenin and Runt-related transcription factor 2 (RUNX2)] and suppressing regulators of other cell fates (such as fat or cartilage). As the cells mature from precursors into functional osteoblasts, they sequentially express specific marker genes (such as alkaline phosphatase, collagen type I α1 chain and osteocalcin). The final outcome for an osteoblast is either programmed cell death or embedding into bone as a lining cell. This mechanically driven process is essential for bone growth and healing in rehabilitation (85-87) (Fig. 2). The net result is a powerful anabolic shift favoring net bone deposition. Therapeutic strategies in rehabilitation leverage this knowledge. Controlled, dynamic loading regimens such as those achieved through specific weight-bearing exercises or low-magnitude, high-frequency vibration are designed to exceed the minimal effective strain threshold needed to initiate this anabolic cascade. This targeted 'mechanotherapy' provides a non-pharmacological means to accelerate fracture callus maturation, enhance bone density around implants and counteract the bone loss associated with immobilization, making it a cornerstone of modern orthopedic rehabilitation (88,89).

6. Chondrocyte mechanobiology in cartilage repair

Chondrocyte mechanobiology is a critical determinant of success or failure in cartilage repair, presenting a unique therapeutic paradox (90,91). Residing within an avascular, aneural ECM, chondrocytes are sensitive to their mechanical environment (92). The application of physiological dynamic compression and hydrostatic pressure, mimicking joint loading during movement, promotes an anabolic response (67). This stimulates the synthesis of essential matrix components such as aggrecan and type II collagen, crucial for restoring the load-bearing functionality of the tissue (93,94). Such mechanical cues are vital for guiding the chondrogenic differentiation of implanted MSCs in tissue engineering strategies (95,96). However, the beneficial effects are critically dependent on load characteristics. Deviations into abnormal loading patterns, such as high-magnitude impact, shear stress or prolonged static compression, trigger a starkly different, catabolic fate. These detrimental forces activate inflammatory pathways (such as the NF-κB pathway) and upregulate matrix-degrading enzymes (MMPs and ADAMTS), leading to the breakdown of the very matrix regenerative therapies aim to build (97,98). This dichotomy underscores the importance of precise rehabilitative loading. Protocols employing motion therapy and continuous passive motion are designed to deliver pro-anabolic stimuli while meticulously avoiding the destructive shear and inflammatory stress that hinder repair and accelerate post-traumatic osteoarthritis.

7. Mechanotransduction in tendon and ligament healing

Tendon and ligament healing are a mechanosensitive process where the precise application of load is paramount for restoring functional strength and preventing dysfunctional scar tissue (99-101). These densely collagenous, hypovascular tissues rely on mechanotransduction to guide repair (102). Tenocytes and ligament fibroblasts possess an array of mechanosensors, including integrins and stretch-activated ion channels, which detect changes in tension and strain during movement (103). Early, controlled mechanical loading stimulates the production and organized alignment of collagen fibrils, enhancing the tensile properties of the repair and promoting a more regenerative rather than purely

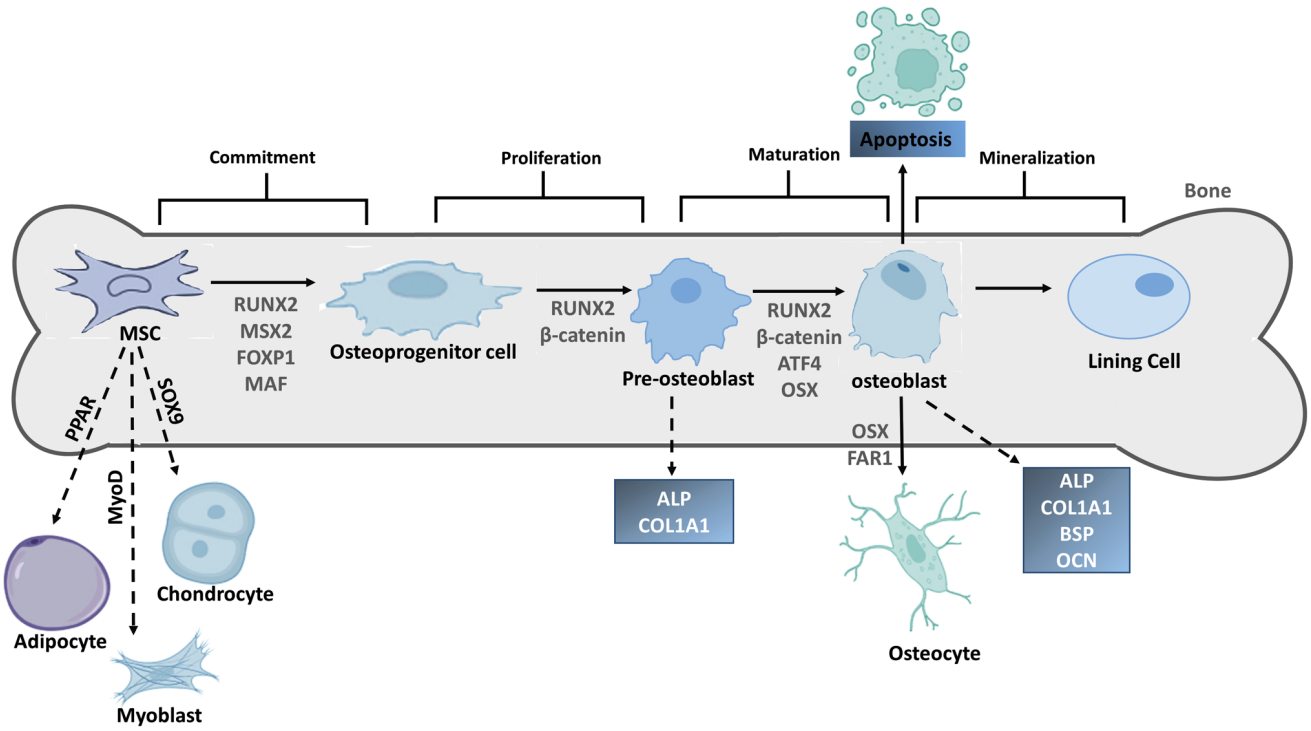

Figure 2. Osteogenic differentiation pathway driven by mechanotransduction. Mechanical signals promote the commitment of MSCs to the osteoblast lineage by activating key transcription factors (such as β-catenin, RUNX2 and MSX2) while inhibiting drivers of alternative fates (such as PPARγ, MyoD and SOX9). The progression from osteoprogenitor to pre-osteoblast to functional osteoblast is marked by the sequential expression of characteristic genes (such as ALP, COL1A1, BSP and OCN). The final fate of the osteoblast is either apoptosis or incorporation into the bone structure as a lining cell. This mechanically-induced osteogenesis is crucial for bone formation and regeneration in orthopedic rehabilitation. MSC, mesenchymal stem cell; PPAR-γ, peroxisome proliferator-activated receptor γ; MyoD, myoblast determination protein; SOX9, SRY-box transcription factor 9; RUNX2, Runt-related transcription factor 2; MSX2, Msh homeobox 2; FOXP1, forkhead box P1, MAF, macrophage-activating factor; ATF4, activating transcription factor 4; FAR1, fatty acyl-CoA reductase 1; ALP, alkaline phosphatase; COL1A1, collagen type I α1 chain; BSP, bone sialoprotein; OCN, osteocalcin; OSX, osterix.

scar-forming outcome (104,105). Conversely, the absence of load (immobilization) leads to tissue atrophy, matrix disorganization and adhesion formation (104). As shown in Fig. 3, physical force is converted into a biochemical signal by bone cells through mechanotransduction, and surface sensors stimulate the intracellular cascade that activates transcription factors to upregulate osteogenic gene expression. However, excessive or premature loading can be equally detrimental, provoking reinjury, inflammation and metaplasia (106). The therapeutic window is narrow. Therefore, rehabilitation protocols are designed to leverage mechanotransduction carefully. Techniques such as early controlled motion and progressive loading regimens apply precise biomechanical cues to activate pro-reparative signaling pathways in tenocytes and resident stem cells. This promotes collagen synthesis and maturation while steering the healing process away from the weak, fibrotic scar tissue that characterizes poor functional recovery, making mechanotherapy a cornerstone of effective tendon and ligament rehabilitation (107,108).

8. Impact of mechanical loading on stem cell differentiation

Mechanical loading is a potent regulator of stem cell fate, serving as a critical determinant in their commitment to specific lineages essential for musculoskeletal repair (30). The differentiation of MSCs is not solely governed by biochemical cues; the physical forces present in their microenvironment provide instructive signals that can override soluble factors (109). For instance, substrate stiffness is a primary mechanical cue. MSCs cultured on substrates mimicking the stiffness of bone tissue tend to undergo osteogenesis, upregulating RUNX2 and osteocalcin expression (110). By contrast, softer substrates that resemble brain or fat tissue promote neurogenesis or adipogenesis, respectively (111). This phenomenon, known as durotaxis, highlights how cells sense and migrate along stiffness gradients, a principle vital for designing biomaterials in tissue engineering (112,113). Beyond static stiffness, dynamic mechanical forces such as cyclic tensile strain, compression and fluid shear stress directly activate mechanosensitive pathways that dictate lineage specification (114,115). Applied cyclic strain promotes tenogenic and osteogenic differentiation by activating pathways such as focal adhesion kinase/MAPK and RhoA/Rho-associated coiled-coil-containing protein kinase, which influence cytoskeletal tension and nuclear translocation of transcription factors (116). Fluid shear stress, crucial in vascular and bone environments, enhances osteogenesis by stimulating prostaglandin release and activating Wnt/β-catenin signaling (117,118). Even low-intensity vibrations have been shown to promote osteogenic differentiation while suppressing adipogenesis, illustrating the finely tuned nature of mechanical input (119). Mechanical forces are transmitted from the cell cytoskeleton (F-actin) to the nucleus through the linker of nucleoskeleton and cytoskeleton complex, causing the nucleus to deform (120). This strain increases the permeability of nuclear pores, allowing for faster import of critical transcription factors (120). As a result, mechanosensitive

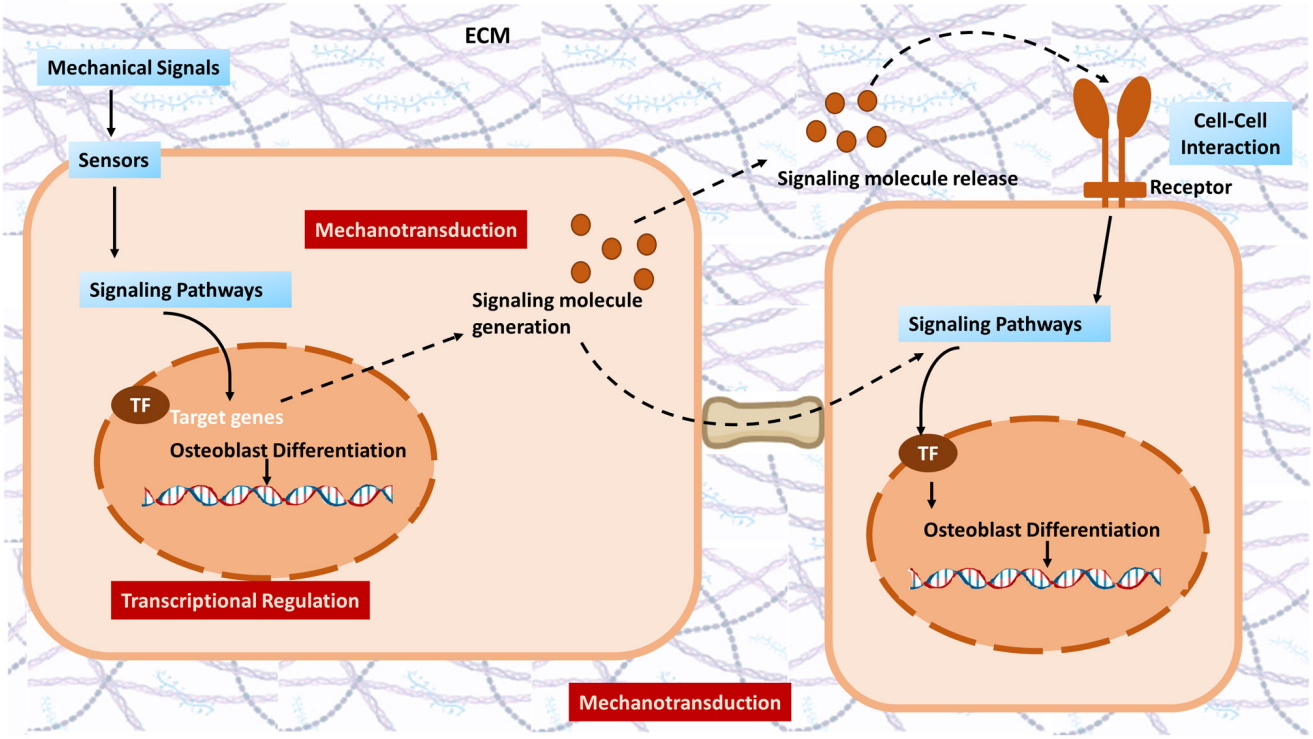

Figure 3. Mechanosignaling in bone cells. This schematic depicts how bone cells perceive mechanical forces and translate them into biological activity, both within themselves and across cell-to-cell junctions. The pathway initiates with mechanical signals being detected by sensors on the cell surface (such as integrins and ion channels) and the cytoskeleton. This triggers mechanotransduction via signaling pathways (such as Hippo and Wnt), leading to the generation of signaling molecules. Intracellularly, key TFs (such as YAP/TAZ, β-catenin and RUNX2) are activated and translocate to the nucleus to mediate transcriptional regulation of target genes (such as BGLAP and SPP1) essential for bone formation. Furthermore, these signals are communicated to neighboring cells via receptor-mediated cell-cell interactions (such as through gap junctions or paracrine signaling), coordinating a synchronized anabolic response across the bone tissue. ECM; extracellular matrix; TF, transcription factor; YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; RUNX2, Runt-related transcription factor 2; BGLAP, bone γ-carboxyglutamate protein; SPP1, secreted phosphoprotein 1.

regulators such as YAP/TAZ and β-catenin accumulate in the nucleus (121). There, they initiate osteogenic genetic programs. At the same time, phosphorylated RUNX2 binds to DNA, prompting chromatin to remodel into an open state. This open conformation further activates the transcription of genes that are essential for bone formation (Fig. 4). The implications for regenerative medicine are profound. In bioreactors for tissue engineering, mechanical conditioning such as cyclic stretching of tendon grafts or fluid flow perfusion in bone scaffolds is used to pre-condition stem cell-seeded constructs, promoting differentiation and matrix maturation before implantation (122). In clinical rehabilitation, understanding how specific exercise-induced loading regimens influence endogenous stem cell pools can lead to targeted therapies that harness mechanical cues to guide tissue repair, offering a non-invasive strategy to enhance regenerative outcomes in orthopedic healing (123,124).

9. Biomechanical strategies in regenerative medicine

The integration of mechanobiology principles into regenerative medicine has given rise to innovative biomechanical strategies designed to orchestrate tissue repair by harnessing the power of mechanical forces (125,126). These approaches move beyond passive structural support, aiming to actively direct cellular behavior through precisely controlled physical cues. A central strategy involves the development of smart biomaterial scaffolds. These are not inert structures but are engineered with specific mechanical properties such as tunable stiffness, viscoelasticity and microtopography that mimic the native ECM of the target tissue (127,128). For instance, a scaffold designed for bone regeneration is designed to be rigid to promote osteogenesis, while a cartilage scaffold requires a compliant, hydrogel-based environment to support chondrogenesis (129). Furthermore, these scaffolds can be functionalized with tethered bioactive molecules that are mechanically activated upon cell adhesion or scaffold stretching, creating a dynamic feedback loop with resident cells (130,131). Beyond static design, dynamic bioreactor systems are a cornerstone of *in vitro* tissue engineering. These devices apply biomimetic mechanical stimuli including cyclic compression, tensile strain and fluid shear stress to cell-seeded constructs during cultivation (132,133). This process of mechanical preconditioning promotes stem cell differentiation, enhances ECM synthesis and organization and yields a more functional and robust tissue graft prior to implantation (134). For example, tensile bioreactors are used to generate aligned collagen fibers in engineered ligaments, significantly improving their ultimate tensile strength (135,136). Translating these principles to the clinic, advanced mechanotherapy is revolutionizing rehabilitation. Techniques such as ESWT and low-intensity pulsed ultrasound (LIPUS) deliver targeted mechanical energy to injury sites, activating pro-regenerative mechanotransduction pathways, enhancing angiogenesis and

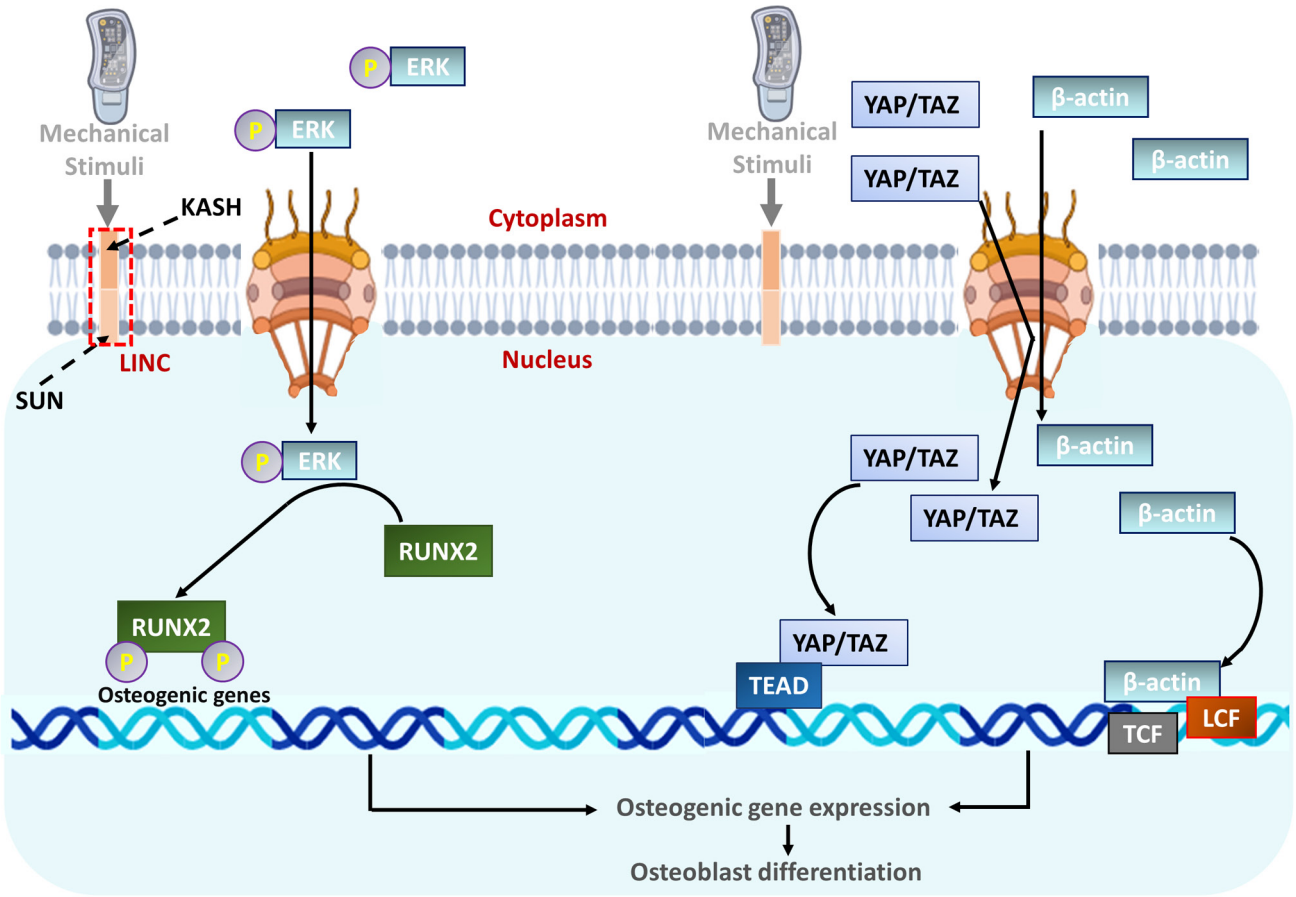

Figure 4. Nuclear mechanotransduction drives osteogenic transcription. Mechanical forces are transduced from the cytoskeleton (F-actin) to the nucleus via the LINC complex, inducing nuclear deformation. This strain enhances the permeability of nuclear pore complexes, facilitating the accelerated nuclear import of key transcription factors and coactivators. The mechanosensitive regulators YAP/TAZ and β-catenin accumulate within the nucleus, where they orchestrate the upregulation of osteogenic gene programs. Concurrently, phosphorylated RUNX2 binds to target sites, inducing chromatin remodeling to an open conformation, which further potentiates the transcriptional activation of genes essential for bone formation. LINC; linker of nucleoskeleton and cytoskeleton; SUN, Sad1-UNC-84 homology; KASH, Klarsicht, ANC-1, syne homology; ERK, extracellular signal-regulated kinase; YAP, Yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; RUNX2, runt-related transcription factor 2; TCF, T-cell factor; LEF, lymphoid enhancer factor; LCF, transcription cofactor; TEAD, transcriptional enhanced associate domain.

stimulating stem cell recruitment (137,138). These biomechanical strategies, which work in concert with biological cues, represent a paradigm shift from merely replacing damaged tissue to actively instructing the innate healing mechanisms of the body, thereby significantly improving functional outcomes in orthopedic rehabilitation (139,140).

10. Physical therapies and exercise-induced mechanotransduction

Physical therapies represent the deliberate clinical application of mechanotransduction principles, utilizing controlled mechanical stimuli to directly influence cellular behavior and guide tissue repair (25,141). Therapeutic exercise is not merely about strengthening muscles; it is a precise modality that delivers targeted biomechanical cues to injured bones, cartilage, tendons and ligaments (25,142). Each movement, whether it is weight-bearing, resistance training or dynamic motion, generates specific forces that are detected by cellular mechanosensors, such as integrins and ion channels (1). This initiates intracellular signaling cascades that promote anabolic processes, including collagen synthesis, matrix organization and stem cell differentiation (143,144). The efficacy of these interventions hinges on the careful calibration of mechanical dosing. Rehabilitation protocols are designed to apply loads within a therapeutic window that stimulate repair without exacerbating damage. For instance, eccentric loading of tendons promotes aligned collagen fibril formation, while controlled motion following cartilage procedures delivers essential dynamic compression that enhances chondrocyte activity and nutrient diffusion (23,145). By harnessing the body's innate responsiveness to physical forces, exercise-based therapies provide a powerful, non-invasive strategy to optimize the regenerative microenvironment, making them a cornerstone of modern orthopedic rehabilitation.

11. Clinical applications in orthopedic rehabilitation

The principles of mechanotransduction are directly applied in orthopedic rehabilitation to enhance healing and functional recovery (7,25). Clinicians utilize controlled mechanical loading through tailored exercise regimens to stimulate cellular repair processes across various tissues. Following fracture fixation, progressive weight-bearing is prescribed

Table II. Clinical applications of mechanotransduction in orthopedic rehabilitation.

Tissue	Clinical application or therapy	Mechanism of action (based on mechanotransduction)	Intended outcome	(Refs.)
Bone	Controlled weight-bearing and low-magnitude high-frequency vibration	Generates interstitial fluid flow and shear stress, detected by osteocytes. Inhibits sclerostin, activating Wnt/β-catenin pathway to promote bone formation.	Accelerate fracture healing and mitigate osteoporosis-related bone loss.	(81,82,153)
Cartilage	Motion therapy and continuous passive motion	Applies dynamic compression and hydrostatic pressure to chondrocytes. Upregulates anabolic factors (such as aggrecan, collagen II) and suppresses catabolic enzymes (such as matrix metalloproteinases).	Enhance cartilage repair, support chondrogenesis and prevent adhesions and degeneration.	(154,155)
Tendon and ligament	Eccentric strengthening exercises and progressive loading	Applies controlled tensile strain detected by tenocytes via integrins and ion channels. Promotes aligned collagen fibril formation and improves tensile strength.	Improve collagen alignment, enhance tensile properties of repair and prevent dysfunctional scarring and atrophy.	(156)
General (multiple tissues)	Low-intensity pulsed ultrasound and extracorporeal shockwave therapy	Deliver targeted mechanical energy (sound waves and shockwaves) to the injury site. Activates pro-regenerative mechanosensitive pathways, enhances angiogenesis and stimulates stem cell recruitment.	Stimulate tissue repair, accelerate healing and treat delayed unions or non-unions.	(138,157)
Tissue engineering	Bioreactor conditioning (such as cyclic strain and compression)	Applies biomimetic mechanical stimuli to stem cell-seeded constructs *in vitro*. Directs stem cell differentiation and promotes extracellular matrix synthesis and organization prior to implantation.	Create more functional and robust engineered tissue grafts (such as bone, cartilage and tendon) with improved mechanical properties.	(31,158)

to generate osteogenic fluid shear stress, promoting callus formation and bone remodeling (146,147). This approach harnesses the mechanosensitivity of osteocytes to guide structural adaptation. In soft tissue injuries, specific loading protocols are fundamental (141,148). For tendinopathies, eccentric strengthening exercises apply controlled tensile strains that upregulate collagen production in tenocytes, improving tendon fibril alignment and tensile strength (149). Similarly, postoperative rehabilitation after cartilage repair procedures incorporates continuous passive motion and carefully graded active exercises (150,151). These interventions deliver essential dynamic compression and hydrostatic pressure to chondrocytes, supporting matrix synthesis while preventing the formation of adhesions and fibrous tissue (23,152). These clinical strategies exemplify mechanotherapy, where externally applied forces are translated into biochemical signals that drive anabolic cellular activity. By modulating the intensity, frequency and type of mechanical stimulus, rehabilitation specialists can optimize the tissue microenvironment to support regeneration, reduce recovery time and improve long-term functional outcomes for patients with musculoskeletal injuries (Table II) (153-158).

12. Mechanotherapy for fracture healing

Mechanotherapy is a targeted therapeutic approach that applies controlled mechanical forces to directly influence the biological process of fracture repair (159,160). Following a fracture, the carefully timed introduction of specific mechanical stimuli is crucial for guiding callus formation, mineralization and eventual remodeling. This strategy harnesses the innate mechanosensitivity of bone cells, particularly osteocytes, which act as primary sensors of changes in their mechanical environment. Clinical applications begin with an initial period of relative stabilization to allow early callus formation, followed by the progressive introduction of load (161). Controlled weight-bearing and resistance exercises are prescribed to generate intermittent hydrostatic pressure and fluid shear stress within the porous network of the bone (162,163). These mechanical cues are detected by osteocytes, triggering

intracellular signaling cascades that downregulate sclerostin expression. The subsequent activation of the Wnt/β-catenin pathway promotes osteoblast differentiation and activity, accelerating bone formation while simultaneously inhibiting osteoclastic bone resorption (53,164). Advanced modalities such as LIPUS and PEMFs provide non-invasive mechanical and electrical stimulation to the fracture site (165). These techniques enhance cellular proliferation, angiogenesis and matrix synthesis, particularly in cases of delayed union or non-union. By precisely modulating the mechanical microenvironment, mechanotherapy offers a powerful, non-pharmacological method to optimize the innate healing capacity of the body, reduce recovery time and improve structural outcomes in fracture management.

13. Mechanically assisted tissue engineering

Mechanically assisted tissue engineering represents a paradigm shift in regenerative medicine, moving beyond passive scaffolds to dynamic systems that actively instruct cellular behavior through applied physical forces. This approach recognizes that mechanical cues are as critical as biochemical signals in directing stem cell differentiation and fostering the development of functional, load-bearing tissues. *In vitro*, this is achieved through the use of bioreactors that deliver biomimetic mechanical conditioning such as cyclic strain for tendons, fluid shear for bone and dynamic compression for cartilage to cell-seeded constructs (166). This preconditioning promotes ECM synthesis, improves structural organization and enhances the mechanical properties of the engineered tissue before implantation. The principles extend to smart scaffold design, where materials are engineered with specific mechanical properties such as tailored stiffness, elasticity and degradability that mimic the native tissue environment and provide ongoing mechanical cues *in vivo* (167). These scaffolds can be designed to respond to body movements, thereby continuously stimulating integrated cells post-implantation. By harnessing mechanotransduction to guide cellular activity at every stage, mechanically assisted tissue engineering creates more robust and biologically integrated grafts, significantly improving their functional outcomes and success rates in orthopedic repair and rehabilitation (125,168).

14. Personalized mechanotransduction-based therapies

The future of orthopedic rehabilitation lies in personalizing interventions based on individual mechanobiological profiles. Personalized mechanotransduction-based therapies move beyond one-size-fits-all protocols by accounting for patient-specific factors such as age, genetics, tissue viability and biomechanics (169). Advanced imaging and diagnostic technologies enable clinicians to assess the unique mechanical microenvironment and cellular responsiveness of the patient, creating a foundation for tailored rehabilitation strategies. For instance, real-time feedback systems and wearable sensors can monitor load distribution and movement patterns during therapeutic exercises. This data, combined with genetic profiling that identifies variations in mechanosensitive pathways, allows for the optimization of mechanical dosing prescribing specific intensities, frequencies and types of loading that are most likely to stimulate anabolic responses in that individual (67). In tissue engineering, this approach translates to 3D-bioprinted scaffolds customized to match the anatomical and mechanical requirements of the patient, potentially seeded with autologous cells primed *ex vivo* using patient-specific mechanical conditioning (170). By aligning therapeutic mechanical inputs with the cellular responsiveness of the individual, these precision interventions maximize regenerative potential, minimize the risk of re-injury and significantly improve functional recovery, heralding a new era of truly personalized orthopedic medicine.

15. Challenges and future directions in optimizing mechanical stimulation protocols

Despite significant advances, translating mechanotransduction research into clinical practice faces notable challenges. A primary hurdle is defining the optimal mechanical dosage, such as the precise intensity, frequency and duration of loading, required to stimulate anabolic repair without provoking catabolic damage or inflammation (171). This therapeutic window varies significantly between tissues, individuals and even stages of healing. Furthermore, the complex, interdependent nature of mechanosignaling pathways makes it difficult to isolate specific therapeutic targets (65). Future progress hinges on developing more sophisticated smart biomaterials that can dynamically respond to *in vivo* mechanical cues and deliver bioactive factors in a feedback-controlled manner (172).

The ultimate objective is to create a closed-loop system where AI-driven algorithms analyze this multifaceted data to prescribe and dynamically adjust mechanical dosing in real-time (173). This will ensure that the stimulus remains within the patient-specific therapeutic window throughout the healing process, which evolves from the inflammatory phase to remodeling. Furthermore, this principle extends to *ex vivo* tissue engineering, where bioreactors can apply patient-specific mechanical conditioning to stem cell-seeded constructs, pre-adapting them to the mechanical demands they will encounter upon implantation (174). By moving beyond a one-size-fits-all model, these optimized, data-driven protocols will maximize regenerative potential, minimize the risk of re-injury and significantly accelerate functional recovery, heralding a new era of precision orthopedics.

16. Conclusion and perspectives

The present review established mechanotransduction as the pivotal mechanism linking mechanical forces to cellular regeneration in orthopedic rehabilitation. The sophisticated interplay between cellular sensors, signaling pathways and the ECM enables physical stimuli to direct tissue repair and adaptation. The translation of these principles into mechanotherapy and biomechanically-informed biomaterials represents a notable advancement beyond traditional rehabilitation. Looking forward, the field must overcome the challenge of defining optimal, personalized mechanical dosing. The future lies in integrating real-time biomechanical monitoring with patient-specific profiling to create dynamic, adaptive treatment protocols. The convergence of smart biomaterials, AI-driven modeling and a deeper systems-level understanding of mechanobiological networks will enable truly predictive

and personalized regenerative interventions. This evolution towards precision mechanotherapy promises to revolutionize musculoskeletal care by optimally harnessing the innate healing mechanisms of the body. This will ultimately enable clinicians to precisely harness the innate mechanoresponsive capacity, offering more effective, non-invasive strategies to restore function and revolutionize patient outcomes in musculoskeletal medicine.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

BW and XZ conceived the review, designed the manuscript writing structure and drafted the manuscript. HL, LL and TL edited and revised the manuscript. YL, QF, YC and BD participated in the literature search and analysis of literature content to be included in the review. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kacprzak B and Stańczak M: Knee Joint Response to MechanicalLoading: Bounding Mechanotransduction with Rehabilitation. 2024. Available from: https://www.preprints.org/manuscript/202409.0995/v1.
2. Sueki D and Brechter J: Orthopedic Rehabilitation Clinical Advisor. 1st edtion. Elsevier Health Sciences, Amsterdam, 2009.
3. d'Agostino M, Craig K, Tibalt E and Respizzi S: Shock wave as biological therapeutic tool: From mechanical stimulation to recovery and healing, through mechanotransduction. Int J Surg 24: 147-153, 2015.
4. Wang N: Review of cellular mechanotransduction. J Phys D Appl Phys 50: 233002, 2017.
5. Yang Y, Wu Y, Zhou K, Wu D, Yao X, Heng BC, Zhou J, Liu H and Ouyang H: Interplay of forces and the immune response for functional tendon regeneration. Front Cell Dev Biol 9: 657621, 2021.
6. Huang X, Das R, Patel A and Duc Nguyen T: Physical stimulations for bone and cartilage regeneration. Regen Eng Transl Med 4: 216-237, 2018.
7. Glatt V, Evans CH and Stoddart MJ: Regenerative rehabilitation: The role of mechanotransduction in orthopaedic regenerative medicine. J Orthop Res 37: 1263-1269, 2019.
8. Gulrandhe P, Acharya S, Phansopkar P and Naqvi W: Exploring the dynamic concept of mechanobiology in regenerative rehabilitation: A narrative review. J Clin Diagn Res 18: KE01-KE04, 2024.
9. Martino F, Perestrelo AR, Vinarský V, Pagliari S and Forte G: Cellular mechanotransduction: From tension to function. Front Physiol 9: 824, 2018.
10. White CR and Frangos JA: The shear stress of it all: The cell membrane and mechanochemical transduction. Philos Trans R Soc Lond B Biol Sci 362: 1459-1467, 2007.
11. Raman N, Imran SAM, Ahmad Amin Noordin KB, Zaman WSWK and Nordin F: Mechanotransduction in mesenchymal stem cells (MSCs) differentiation: A review. Int J Mol Sci 23: 4580, 2022.
12. Xu BY, Jin Y, Ma XH, Wang CY, Guo Y and Zhou D: The potential role of mechanically sensitive ion channels in the physiology, injury, and repair of articular cartilage. J Orthop Surg (Hong Kong) 28: 2309499020950262, 2020.
13. Piersma B, Bank RA and Boersema M: Signaling in fibrosis: TGF-β, WNT, and YAP/TAZ converge. Front Med (Lausanne) 2: 59, 2015.
14. Heng BC, Zhang X, Aubel D, Bai Y, Li X, Wei Y, Fussenegger M and Deng X: An overview of signaling pathways regulating YAP/TAZ activity. Cell Mol Life Sci 78: 497-512, 2021.
15. Jiang L, Li J, Zhang C, Shang Y and Lin J: YAP-mediated crosstalk between the Wnt and Hippo signaling pathways (review). Mol Med Rep 22: 4101-4106, 2020.
16. Xie W, Wei X, Kang H, Jiang H, Chu Z, Lin Y, Hou Y and Wei Q: Static and dynamic: Evolving biomaterial mechanical properties to control cellular mechanotransduction. Adv Sci (Weinh) 10: 2204594, 2023.
17. Wang T, Nanda SS, Papaefthymiou GC and Yi DK: Mechanophysical cues in extracellular matrix regulation of cell behavior. Chembiochem 21: 1254-1264, 2020.
18. Li G: Novel applications of distraction histogenesis. Orthop Proc 107-B (Suppl 9): S85, 2025.
19. Sun Y, Wan B, Wang R, Zhang B, Luo P, Wang D, Nie JJ, Chen D and Wu X: Mechanical stimulation on mesenchymal stem cells and surrounding microenvironments in bone regeneration: Regulations and applications. Front Cell Dev Biol 10: 808303, 2022.
20. Ma Q, Miri Z, Haugen HJ, Moghanian A and Loca D: Significance of mechanical loading in bone fracture healing, bone regeneration, and vascularization. J Tissue Eng 14: 20417314231172573, 2023.
21. Pagnotti GM, Styner M, Uzer G, Patel VS, Wright LE, Ness KK, Guise TA, Rubin J and Rubin CT: Combating osteoporosis and obesity with exercise: Leveraging cell mechanosensitivity. Nat Rev Endocrinol 15: 339-355, 2019.
22. Yu Y, Feng T, Qiu H, Gu Y, Chen Q, Zuo C and Ma H: Simultaneous photoacoustic and ultrasound imaging: A review. Ultrasonics 139: 107277, 2024.
23. Anderson DE and Johnstone B: Dynamic mechanical compression of chondrocytes for tissue engineering: A critical review. Front Bioeng Biotechnol 5: 76, 2017.
24. Li Y, Frank EH, Wang Y, Chubinskaya S, Huang HH and Grodzinsky AJ: Moderate dynamic compression inhibits pro-catabolic response of cartilage to mechanical injury, tumor necrosis factor-α and interleukin-6, but accentuates degradation above a strain threshold. Osteoarthritis Cartilage 21: 1933-1941, 2013.
25. Thompson WR, Scott A, Loghmani MT, Ward SR and Warden SJ: Understanding mechanobiology: Physical therapists as a force in mechanotherapy and musculoskeletal regenerative rehabilitation. Phys Ther 96: 560-569, 2016.
26. Chatterjee M, Muljadi PM and Andarawis-Puri N: The role of the tendon ECM in mechanotransduction: Disruption and repair following overuse. Connect Tissue Res 63: 28-42, 2022.
27. Kjaer M: Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiol Rev 84: 649-698, 2004.
28. Kong W, Lyu C, Liao H and Du Y: Collagen crosslinking: Effect on structure, mechanics and fibrosis progression. Biomed Mater 16: 062005, 2021.
29. Ren C, Liu F, Zhang S, Xu H and Yang P: The role of collagen matrix in the development and progression of heterotopic ossification in tendon and its biological mechanisms. FASEB J 39: e70873, 2025.
30. Vining KH and Mooney DJ: Mechanical forces direct stem cell behaviour in development and regeneration. Nat Rev Mol Cell Biol 18: 728-742, 2017.

31. Liao S, Chan CK and Ramakrishna S: Stem cells and biomimetic materials strategies for tissue engineering. Mater Sci Eng C 28: 1189-1202, 2008.
32. Castro N, Ribeiro S, Fernandes M, Ribeiro C, Cardoso V, Correia V, Minguez R and Lanceros-Mendez S: Physically active bioreactors for tissue engineering applications. Adv Biosyst 4: e2000125, 2020.
33. Rosso F, Bonasia DE, Marmotti A, Cottino U and Rossi R: Mechanical stimulation (pulsed electromagnetic fields 'PEMF' and extracorporeal shock wave therapy 'ESWT') and tendon regeneration: A possible alternative. Front Aging Neurosci 7: 211, 2015.
34. Nosrati H and Nosrati M: Artificial intelligence in regenerative medicine: Applications and implications. Biomimetics (Basel) 8: 442, 2023.
35. Xiao R, Liu J and Xu XS: Mechanosensitive GPCRs and ion channels in shear stress sensing. Curr Opin Cell Biol 84: 102216, 2023.
36. Poole K: The diverse physiological functions of mechanically activated ion channels in mammals. Annu Rev Physiol 84: 307-329, 2022.
37. Janmey PA: The cytoskeleton and cell signaling: Component localization and mechanical coupling. Physiol Rev 78: 763-781, 1998.
38. Schwartz MA: Integrins and extracellular matrix in mechanotransduction. Cold Spring Harb Perspect Biol 2: a005066, 2010.
39. Kechagia JZ, Ivaska J and Roca-Cusachs P: Integrins as biomechanical sensors of the microenvironment. Nat Rev Mol Cell Biol 20: 457-473, 2019.
40. Verbruggen SW, Sittichokechaiwut A and Reilly GC: Osteocytes and primary cilia. Curr Osteoporos Rep 21: 719-730, 2023.
41. Varelas X: The Hippo pathway effectors TAZ and YAP in development, homeostasis and disease. Development 141: 1614-1626, 2014.
42. Kwon H, Kim J and Jho Eh: Role of the Hippo pathway and mechanisms for controlling cellular localization of YAP/TAZ. FEBS J 289: 5798-5818, 2022.
43. Garcin CL and Habib SJ: A comparative perspective on Wnt/β-catenin signalling in cell fate determination. Asymmetric Cell Division in Development, Differentiation and Cancer, Results and Problems in Cell Differentiation. Springer International Publishing, Cham, pp323-350, 2017.
44. Shah N, Morsi Y and Manasseh R: From mechanical stimulation to biological pathways in the regulation of stem cell fate. Cell Biochem Funct 32: 309-325, 2014.
45. Van Helvert S, Storm C and Friedl P: Mechanoreciprocity in cell migration. Nat Cell Biol 20: 8-20, 2018.
46. Murrell M, Oakes PW, Lenz M and Gardel ML: Forcing cells into shape: The mechanics of actomyosin contractility. Nat Rev Mol Cell Biol 16: 486-498, 2015.
47. Butler DL, Goldstein SA, Guldberg RE, Guo XE, Kamm R, Laurencin CT, McIntire LV, Mow VC, Nerem RM, Sah RL, *et al*: The impact of biomechanics in tissue engineering and regenerative medicine. Tissue Eng Part B Rev 15: 477-484, 2009.
48. Ramage L: Integrins and extracellular matrix in mechanotransduction. Cell Health Cytoskelet 4: 1-9, 2012.
49. Kanchanawong P and Calderwood DA: Organization, dynamics and mechanoregulation of integrin-mediated cell-ECM adhesions. Nat Rev Mol Cell Biol 24: 142-161, 2023.
50. Li J, Huang S and Chen H: Advances in imaging techniques for mammalian/human ciliated cell's cilia: Insights into structure, function, and dynamics. Biology (Basel) 14: 521, 2025.
51. Abou Alaiwi WA, Lo ST and Nauli SM: Primary cilia: Highly sophisticated biological sensors. Sensors (Basel) 9: 7003-7020, 2009.
52. Piccolo S, Dupont S and Cordenonsi M: The biology of YAP/TAZ: Hippo signaling and beyond. Physiol Rev 94: 1287-1312, 2014.
53. Hu L, Chen W, Qian A and Li YP: Wnt/β-catenin signaling components and mechanisms in bone formation, homeostasis, and disease. Bone Res 12: 39, 2024.
54. Duan P and Bonewald L: The role of the wnt/β-catenin signaling pathway in formation and maintenance of bone and teeth. Int J Biochem Cell Biol 77: 23-29, 2016.
55. Etienne-Manneville S: Actin and microtubules in cell motility: Which one is in control? Traffic 5: 470-477, 2004.
56. Hohmann T and Dehghani F: The cytoskeleton-a complex interacting meshwork. Cells 8: 362, 2019.
57. Mierke CT: Extracellular matrix cues regulate mechanosensing and mechanotransduction of cancer cells. Cells 13: 96, 2024.
58. Vincent LG, Choi YS, Alonso-Latorre B, del Álamo JC and Engler AJ: Mesenchymal stem cell durotaxis depends on substrate stiffness gradient strength. Biotechnol J 8: 472-484, 2013.
59. Chaudhuri O, Cooper-White J, Janmey PA, Mooney DJ and Shenoy VB: Effects of extracellular matrix viscoelasticity on cellular behaviour. Nature 584: 535-546, 2020.
60. Berdiaki A, Neagu M, Tzanakakis P, Spyridaki I, Pérez S and Nikitovic D: Extracellular matrix components and mechanosensing pathways in health and disease. Biomolecules 14: 1186, 2024.
61. Teixeira SPB, Domingues RMA, Shevchuk M, Gomes ME, Peppas NA and Reis RL: Biomaterials for sequestration of growth factors and modulation of cell behavior. Adv Funct Mater 30: 1909011, 2020.
62. Cipitria A and Salmeron-Sanchez M: Mechanotransduction and growth factor signalling to engineer cellular microenvironments. Adv Healthc Mater 6: 1700052, 2017.
63. Hinz B: The extracellular matrix and transforming growth factor-β1: Tale of a strained relationship. Matrix Biol 47: 54-65, 2015.
64. Selig M, Lauer JC, Hart ML and Rolauffs B: Mechanotransduction and stiffness-sensing: Mechanisms and opportunities to control multiple molecular aspects of cell phenotype as a design cornerstone of cell-instructive biomaterials for articular cartilage repair. Int J Mol Sci 21: 5399, 2020.
65. Hodgkinson T, Kelly DC, Curtin CM and O'Brien FJ: Mechanosignalling in cartilage: An emerging target for the treatment of osteoarthritis. Nat Rev Rheumatol 18: 67-84, 2022.
66. Zhao Z, Li Y, Wang M, Zhao S, Zhao Z and Fang J: Mechanotransduction pathways in the regulation of cartilage chondrocyte homoeostasis. J Cell Mol Med 24: 5408-5419, 2020.
67. Ozcivici E, Luu YK, Adler B, Qin YX, Rubin J, Judex S and Rubin CT: Mechanical signals as anabolic agents in bone. Nat Rev Rheumatol 6: 50-59, 2010.
68. Klein-Nulend J and Bakker AD: Osteocytes: Mechanosensors of bone and orchestrators of mechanical adaptation. Clin Rev Bone Miner Metab 5: 195-209, 2007.
69. Ganesh T, Laughrey LE, Niroobakhsh M and Lara-Castillo N: Multiscale finite element modeling of mechanical strains and fluid flow in osteocyte lacunocanalicular system. Bone 137: 115328, 2020.
70. Wu Z, Li W, Jiang K, Lin Z, Qian C, Wu M, Xia Y, Li N, Zhang H, Xiao H, *et al*: Regulation of bone homeostasis: Signaling pathways and therapeutic targets. MedComm (2020) 5: e657, 2024.
71. Gao Y, Chen N, Fu Z and Zhang Q: Progress of Wnt signaling pathway in osteoporosis. Biomolecules 13: 483, 2023.
72. Nguyen MT, Gronthos S, Zhao Y, Chandrakanthan V, Truong VK and Vasilev K: Overcoming challenges in cartilage regeneration: The role of chondrogenic inducers. Bioeng Transl Med: e70079, 2025.
73. Guilak F and Hung CT: Physical regulation of cartilage metabolism. In: Basic Orthopaedic Biomechanics & Mechano-Biology. Mow VC and Huiskes R (eds). Lippincott Williams & Wilkins, Philadelphia, PA, p259, 2005.
74. Iseki T, Rothrauff BB, Kihara S, Sasaki H, Yoshiya S, Fu FH, Tuan RS and Gottardi R: Dynamic compressive loading improves cartilage repair in an in vitro model of microfracture: Comparison of 2 mechanical loading regimens on simulated microfracture based on fibrin gel scaffolds encapsulating connective tissue progenitor cells. Am J Sports Med 47: 2188-2199, 2019.
75. Shi HF, Cheung WH, Qin L, Leung AHC and Leung KS: Low-magnitude high-frequency vibration treatment augments fracture healing in ovariectomy-induced osteoporotic bone. Bone 46: 1299-1305, 2010.
76. Frank C, Akeson WH, Woo SL, Amiel D and Coutts RD: Physiology and therapeutic value of passive joint motion. Clin Orthop Relat Res: 113-125, 1984.
77. Mellon SJ and Tanner K: Bone and its adaptation to mechanical loading: A review. Int Mater Rev 57: 235-255, 2012.
78. Pivonka P, Park A and Forwood MR: Functional adaptation of bone: The mechanostat and beyond. In: Multiscale Mechanobiology of Bone Remodeling and Adaptation. CISM International Centre for Mechanical Sciences. Pivonka P (eds). Vol 578. Springer, Heidelberg, pp1-60, 2017.
79. Augat P, Simon U, Liedert A and Claes L: Mechanics and mechano-biology of fracture healing in normal and osteoporotic bone. Osteoporos Int 16 (Suppl 2): S36-S43, 2005.
80. Yu W, Ou R, Hou Q, Li C, Yang X, Ma Y, Wu X and Chen W: Multiscale interstitial fluid computation modeling of cortical bone to characterize the hydromechanical stimulation of lacunar-canalicular network. Bone 193: 117386, 2025.

81. Marini F, Giusti F, Palmini G and Brandi ML: Role of Wnt signaling and sclerostin in bone and as therapeutic targets in skeletal disorders. Osteoporos Int 34: 213-238, 2023.
82. Burgers TA and Williams BO: Regulation of Wnt/β-catenin signaling within and from osteocytes. Bone 54: 244-249, 2013.
83. Arya PN, Saranya I and Selvamurugan N: Crosstalk between Wnt and bone morphogenetic protein signaling during osteogenic differentiation. World J Stem Cells 16: 102-113, 2024.
84. Honma M, Ikebuchi Y, Kariya Y and Suzuki H: Regulatory mechanisms of RANKL presentation to osteoclast precursors. Curr Osteoporos Rep 12: 115-120, 2014.
85. Sun Y, Yuan Y, Wu W, Lei L and Zhang L: The effects of locomotion on bone marrow mesenchymal stem cell fate: Insight into mechanical regulation and bone formation. Cell Biosci 11: 88, 2021.
86. Chan WCW, Tan Z, To MKT and Chan D: Regulation and role of transcription factors in osteogenesis. Int J Mol Sci 22: 5445, 2021.
87. James AW: Review of signaling pathways governing MSC osteogenic and adipogenic differentiation. Scientifica (Cairo) 2013: 684736, 2013.
88. Ozdemir F, Zateri C and Murat S: Evaluation of the efficacy of therapeutic ultrasound on bone mineral density in postmenopausal period. Rheumatol Int 28: 361-365, 2008.
89. Popa M, Cursaru A, Cretu B, Iordache S, Iacobescu GL, Spiridonica R, Serban B and Cirstoiu C: Enhancing osteoporosis management: A thorough examination of surgical techniques and their effects on patient outcomes. Cureus 16: e59681, 2024.
90. Muthu S, Korpershoek JV, Novais EJ, Tawy GF, Hollander AP and Martin I: Failure of cartilage regeneration: Emerging hypotheses and related therapeutic strategies. Nat Rev Rheumatol 19: 403-416, 2023.
91. Oliveira S, Hinckel BB, Silva FS, Carvalho Ó and Leal A: A guide to articular cartilage functioning: A comprehensive review, current challenges and mechanobiological solutions. Prog Biomed Eng (Bristol) 7, 2025.
92. Statham P, Jones E, Jennings LM and Fermor HL: Reproducing the biomechanical environment of the chondrocyte for cartilage tissue engineering. Tissue Eng Part B Rev 28: 405-420, 2022.
93. Kjær M, Langberg H, Heinemeier K, Bayer ML, Hansen M, Holm L, Doessing S, Kongsgaard M, Krogsgaard MR and Magnusson SP: From mechanical loading to collagen synthesis, structural changes and function in human tendon. Scand J Med Sci Sports 19: 500-510, 2009.
94. Responte DJ, Natoli RM and Athanasiou KA: Collagens of articular cartilage: Structure, function, and importance in tissue engineering. Crit Rev Biomed Eng 35: 363-411, 2007.
95. Fahy N, Alini M and Stoddart MJ: Mechanical stimulation of mesenchymal stem cells: Implications for cartilage tissue engineering. J Orthop Res 36: 52-63, 2018.
96. Kelly DJ and Jacobs CR: The role of mechanical signals in regulating chondrogenesis and osteogenesis of mesenchymal stem cells. Birth Defects Res C Embryo Today 90: 75-85, 2010.
97. Fang T, Zhou X, Jin M, Nie J and Li X: Molecular mechanisms of mechanical load-induced osteoarthritis. Int Orthop 45: 1125-1136, 2021.
98. Li T, Peng J, Li Q, Shu Y, Zhu P and Hao L: The mechanism and role of ADAMTS protein family in osteoarthritis. Biomolecules 12: 959, 2022.
99. Jiang F, Zhao H, Zhang P, Bi Y, Zhang H, Sun S, Yao Y, Zhu X, Yang F, Liu Y, *et al*: Challenges in tendon-bone healing: emphasizing inflammatory modulation mechanisms and treatment. Front Endocrinol (Lausanne) 15: 1485876, 2024.
100. Killian ML, Cavinatto L, Galatz LM and Thomopoulos S: The role of mechanobiology in tendon healing. J Shoulder Elbow Surg 21: 228-237, 2012.
101. Woo SLY, Nguyen TD, Papas N and Liang R: Tissue mechanics of ligaments and tendons. In: Biomechanics in ergonomics. 2nd edition. CRC Press, pp127-148, 2007.
102. Fu S, Panayi A, Fan J, Mayer HF, Daya M, Khouri RK, Gurtner GC, Ogawa R and Orgill DP: Mechanotransduction in wound healing: from the cellular and molecular level to the clinic. Adv Skin Wound Care 34: 67-74, 2021.
103. Li Y, Wu T and Liu S: Identification and distinction of tenocytes and tendon-derived stem cells. Front Cell Dev Biol 9: 629515, 2021.
104. Montgomery J: Building a better scar: Re-engineering extracellular matrix structure in dermal scars. Virginia Polytechnic Institute, 2020.
105. Buff-Lindner AH: The Role of Poly N Acetyl Glucosamine Nanofibers in Cutaneous Wound Healing. Baishideng Publishing Group Inc., Pleasanton, CA, 2014.
106. Aicale R, Tarantino D and Maffulli N: Overuse injuries in sport: A comprehensive overview. J Orthop Surg Res 13: 309, 2018.
107. El Ayadi A, Jay JW and Prasai A: Current approaches targeting the wound healing phases to attenuate fibrosis and scarring. Int J Mol Sci 21: 1105, 2020.
108. Sephel GC and Woodward SC: Repair, Regeneration, and Fibrosis. Lippincott, Williams & Wilkins, Baltimore, pp84-117, 2001.
109. Huang C, Dai J and Zhang XA: Environmental physical cues determine the lineage specification of mesenchymal stem cells. Biochim Biophys Acta 1850: 1261-1266, 2015.
110. El-Rashidy AA, El Moshy S, Radwan IA, Rady D, Abbass MMS, Dörfer CE and Fawzy El-Sayed KM: Effect of polymeric matrix stiffness on osteogenic differentiation of mesenchymal stem/progenitor cells: Concise review. Polymers (Basel) 13: 2950, 2021.
111. Lee J, Abdeen AA, Tang X, Saif TA and Kilian KA: Matrix directed adipogenesis and neurogenesis of mesenchymal stem cells derived from adipose tissue and bone marrow. Acta Biomater 42: 46-55, 2016.
112. Espina JA, Marchant CL and Barriga EH: Durotaxis: The mechanical control of directed cell migration. FEBS J 289: 2736-2754, 2022.
113. Aubry D, Gupta M, Ladoux B and Allena R: Mechanical link between durotaxis, cell polarity and anisotropy during cell migration. Phys Biol 12: 026008, 2015.
114. Fang Y, Wu D and Birukov KG: Mechanosensing and mechanoregulation of endothelial cell functions. Compr Physiol 9: 873-904, 2019.
115. Chen JC and Jacobs CR: Mechanically induced osteogenic lineage commitment of stem cells. Stem Cell Res Ther 4: 107, 2013.
116. Niu H, Lin D, Tang W, Ma Y, Duan B, Yuan Y and Liu C: Surface topography regulates osteogenic differentiation of MSCs via crosstalk between FAK/MAPK and ILK/β-catenin pathways in a hierarchically porous environment. ACS Biomater Sci Eng 3: 3161-3175, 2017.
117. Jia YY, Li F, Geng N, Gong P, Huang SJ, Meng LX, Lan J and Ban Y: Fluid flow modulates the expression of genes involved in the Wnt signaling pathway in osteoblasts in 3D culture conditions. Int J Mol Med 33: 1282-1288, 2014.
118. Alfieri R, Vassalli M and Viti F: Flow-induced mechanotransduction in skeletal cells. Biophys Rev 11: 729-743, 2019.
119. Baskan O, Mese G and Ozcivici E: Low-intensity vibrations normalize adipogenesis-induced morphological and molecular changes of adult mesenchymal stem cells. Proc Inst Mech Eng H 231: 160-168, 2017.
120. Kloc M and Wosik J: Mechanical forces, nucleus, chromosomes, and chromatin. Biomolecules 15: 354, 2025.
121. Cai X, Wang KC and Meng Z: Mechanoregulation of YAP and TAZ in cellular homeostasis and disease progression. Front Cell Dev Biol 9: 673599, 2021.
122. Ahata B, Kan T, Serefoglu Gun B, Tanyeri Y, Oktay B, Oktay A and Koc RC: Bioreactors for tissue engineering. In: Biomaterials and Tissue Engineering. Gunduz O, Egles C, Pérez RA, Ficai D and Ustundag CB (eds). Springer International Publishing, Cham, pp259-303, 2023.
123. Chen J, Zhou R, Feng Y and Cheng L: Molecular mechanisms of exercise contributing to tissue regeneration. Signal Transduct Target Ther 7: 383, 2022.
124. Head PL: Rehabilitation considerations in regenerative medicine. Phys Med Rehabil Clin N Am 27: 1043-1054, 2016.
125. Kim S, Uroz M, Bays JL and Chen CS: Harnessing mechanobiology for tissue engineering. Dev Cell 56: 180-191, 2021.
126. Shafiq M, Ali O, Han SB and Kim DH: Mechanobiological strategies to enhance stem cell functionality for regenerative medicine and tissue engineering. Front Cell Dev Biol 9: 747398, 2021.
127. Xia T, Liu W and Yang L: A review of gradient stiffness hydrogels used in tissue engineering and regenerative medicine. J Biomed Mater Res A 105: 1799-1812, 2017.
128. Janson IA and Putnam AJ: Extracellular matrix elasticity and topography: Material-based cues that affect cell function via conserved mechanisms. J Biomed Mater Res A 103: 1246-1258, 2015.
129. Song J, Li L, Fang L, Zhang E, Zhang Y, Zhang Z, Vangari P, Huang Y, Tian F, Zhao Y, *et al*: Advanced strategies of scaffolds design for bone regeneration. BMEMat 1: e12046, 2023.
130. Kim TG, Shin H and Lim DW: Biomimetic scaffolds for tissue engineering†. Adv Funct Mater 22: 2446-2468, 2012.

131. Monemian Esfahani A, Rosenbohm J, Reddy K, Jin X, Bouzid T, Riehl B, Kim E, Lim JY and Yang R: Tissue regeneration from mechanical stretching of cell-cell adhesion. Tissue Eng Part C Methods 25: 631-640, 2019.
132. Huang G, Li F, Zhao X, Ma Y, Li Y, Lin M, Jin G, Lu TJ, Genin GM and Xu F: Functional and biomimetic materials for engineering of the three-dimensional cell microenvironment. Chem Rev 117: 12764-12850, 2017.
133. Badekila AK, Kini S and Jaiswal AK: Fabrication techniques of biomimetic scaffolds in three-dimensional cell culture: A review. J Cell Physiol 236: 741-762, 2021.
134. Schumann D, Kujat R, Nerlich M and Angele P: Mechanobiological conditioning of stem cells for cartilage tissue engineering. Biomed Mater Eng 16 (Suppl 4): S37-S52, 2006.
135. Wang T, Gardiner BS, Lin Z, Rubenson J, Kirk TB, Wang A, Xu J, Smith DW, Lloyd DG and Zheng MH: Bioreactor design for tendon/ligament engineering. Tissue Eng Part B Rev 19: 133-146, 2013.
136. Lim WL, Liau LL, Ng MH, Chowdhury SR and Law JX: Current progress in tendon and ligament tissue engineering. Tissue Eng Regen Med 16: 549-571, 2019.
137. Qin H, Du L, Luo Z, He Z, Wang Q, Chen S and Zhu YL: The therapeutic effects of low-intensity pulsed ultrasound in musculoskeletal soft tissue injuries: Focusing on the molecular mechanism. Front Bioeng Biotechnol 10: 1080430, 2022.
138. Lei L, Zhang Q, Du M and Li L: Mechanoregulation of cell fate by low-intensity pulsed ultrasound: Mechanisms and advances in regenerative medicine. BIO Integr 6: 1-18, 2025.
139. Malik S: The physics of the human body: Biomechanics and beyond. Worldw J Phys 1: 53-63, 2020.
140. Glatt V, Evans CH and Tetsworth K: A concert between biology and biomechanics: The influence of the mechanical environment on bone healing. Front Physiol 7: 678, 2017.
141. Ng JL, Kersh ME, Kilbreath S and Knothe Tate M: Establishing the basis for mechanobiology-based physical therapy protocols to potentiate cellular healing and tissue regeneration. Front Physiol 8: 303, 2017.
142. Khan KM and Scott A: Mechanotherapy: How physical therapists' prescription of exercise promotes tissue repair. Br J Sports Med 43: 247-252, 2009.
143. Xiao Z and Quarles LD: Physiological mechanisms and therapeutic potential of bone mechanosensing. Rev Endocr Metab Disord 16: 115-129, 2015.
144. Mobasheri A, Carter SD, Martín-Vasallo P and Shakibaei M: Integrins and stretch activated ion channels; putative components of functional cell surface mechanoreceptors in articular chondrocytes. Cell Biol Int 26: 1-18, 2002.
145. Lambrianides Y: Temporal Dynamics of Muscle and Tendon Adaptation to Mechano-Metabolic Stimuli. London South Bank University, 2024.
146. Beeharry MW and Ahmad B: Principles of fracture healing and fixation: A literature review. Cureus 16: e76250, 2024.
147. Thakur AJ: The Elements of Fracture Fixation. 4th edition. Elsevier Health Sciences, India, 2019.
148. Qin YX and Zhao J: Mechanobiology in cellular, molecular, and tissue adaptation. Mechanobiol Med 1: 100022, 2023.
149. Pourshafie S, Ashnagar Z, Jalaie S and Bashardoust Tajali S: Effects of eccentric exercises with and without dry needling approaches at the patients with chronic rotator cuff tendinopathy. J Bodyw Mov Ther 42: 976-981, 2025.
150. Fazalare JA, Griesser MJ, Siston RA and Flanigan DC: The use of continuous passive motion following knee cartilage defect surgery: A systematic review. Orthopedics 33: 878, 2010.
151. Howard JS, Mattacola CG, Romine SE and Lattermann C: Continuous passive motion, early weight bearing, and active motion following knee articular cartilage repair: Evidence for clinical practice. Cartilage 1: 276-286, 2010.
152. Elder BD and Athanasiou KA: Hydrostatic pressure in articular cartilage tissue engineering: From chondrocytes to tissue regeneration. Tissue Eng Part B Rev 15: 43-53, 2009.
153. Bonewald LF and Johnson ML: Osteocytes, mechanosensing and Wnt signaling. Bone 42: 606-615, 2008.
154. ur Rehman S, Iqbal S, Shahid MU, Jahangir MS and Malik AL: Cartilage: Structure, function, and the pathogenesis of osteoarthritis. In: Advancements in Synovial Joint Science-Structure, Function, and Beyond. IntechOpen, London, 2024.
155. Houpt JB, Gahunia HK and Pritzker KPH: Physical and rehabilitative therapy for knee articular cartilage injury and disease. In: Articular Cartilage of the Knee: Health, Disease and Therapy. Springer, New York, NY, pp235-251, 2020.
156. Galloway MT, Lalley AL and Shearn JT: The role of mechanical loading in tendon development, maintenance, injury, and repair. J Bone Joint Surg Am 95: 1620-1628, 2013.
157. Gonçalves AI, Righelli L, Reis RL, El Haj AJ and Gomes ME: Understanding degeneration and healing pathways for tissue engineered treatment strategies in tendinopathy. Cells Tissues Organs 214: 459-476, 2025.
158. Burdick JA and Vunjak-Novakovic G: Engineered microenvironments for controlled stem cell differentiation. Tissue Eng Part A 15: 205-219, 2009.
159. McKay J, Nasb M and Hafsi K: Mechanobiology-based physical therapy and rehabilitation after orthobiologic interventions: A narrative review. Int Orthop 46: 179-188, 2022.
160. Benulič Č, Canton G, Rasio N, Murena L and Kristan A: Mechanobiology of indirect bone fracture healing under conditions of relative stability: A narrative review for the practicing clinician. Acta Biomed 92: e2021582, 2022.
161. Claes L, Eckert-Hübner K and Augat P: The effect of mechanical stability on local vascularization and tissue differentiation in callus healing. J Orthop Res 20: 1099-1105, 2002.
162. Zhang B, Mateus J and Hargens A: Osteoporosis, circulation, and fluid dynamics. In: Skeletal Circulation in Clinical Practice. World Scientific, pp253-282, 2016.
163. Zernicke R, MacKay C and Lorincz C: Mechanisms of bone remodeling during weight-bearing exercise. Appl Physiol Nutr Metab 31: 655-660, 2006.
164. Wang X, Tian Y, Liang X, Yin C, Huai Y, Zhao Y, Huang Q, Chu X, Wang W and Qian A: Bergamottin promotes osteoblast differentiation and bone formation via activating the Wnt/β-catenin signaling pathway. Food Funct 13: 2913-2924, 2022.
165. Walker NA, Denegar CR and Preische J: Low-intensity pulsed ultrasound and pulsed electromagnetic field in the treatment of tibial fractures: A systematic review. J Athl Train 42: 530-535, 2007.
166. Li K, Zhang C, Qiu L, Gao L and Zhang X: Advances in application of mechanical stimuli in bioreactors for cartilage tissue engineering. Tissue Eng Part B Rev 23: 399-411, 2017.
167. Carotenuto F, Politi S, Ul Haq A, De Matteis F, Tamburri E, Terranova ML, Teodori L, Pasquo A and Di Nardo P: From soft to hard biomimetic materials: Tuning micro/nano-architecture of scaffolds for tissue regeneration. Micromachines (Basel) 13: 780, 2022.
168. Rajendran AK, Sankar D, Amirthalingam S, Kim HD, Rangasamy J and Hwang NS: Trends in mechanobiology guided tissue engineering and tools to study cell-substrate interactions: A brief review. Biomater Res 27: 55, 2023.
169. Han HM, Kim SY and Kim DH: Mechanotransduction for therapeutic approaches: Cellular aging and rejuvenation. APL Bioeng 9: 021502, 2025.
170. Akilbekova D and Turlybekuly A: Patient-specific 3D bioprinting for in situ tissue engineering and regenerative medicine. In: 3D Printing in Medicine. Elsevier, New York, NY, pp149-178, 2023.
171. Behringer M, Heinrich C and Franz A: Anabolic signals and muscle hypertrophy-significance for strength training in sports medicine. Sports Orthop Traumatol 41: 9-18, 2025.
172. Raman R and Langer R: Biohybrid design gets personal: New materials for patient-specific therapy. Adva Mater 32: e1901969, 2020.
173. Soumya MAAK: AI-driven insights: Revolutionizing health diagnostics and treatment. Budha Publication, Tamil, Nadu, 2024.
174. Gantenbein B, Frauchiger DA, May RD, Bakirci E, Rohrer U and Grad S: Developing bioreactors to host joint-derived tissues that require mechanical stimulation. In: Encyclopedia of Tissue Engineering and Regenerative Medicine. Elsevier, New York, NY, pp261-280, 2019.