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Editorial

Mechanobiology in cellular, molecular, and tissue adaptation

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ABSTRACT

The use of mechanical biology and biomechanical signal transduction is a novel approach to attenuate biological tissue degeneration, whereas the understanding of specific cellular responses is critical to delineate the underlying mechanism. Dynamic mechanical signals with optimized loading signals, i.e., intensity and frequency, have been shown to have the potential to regulate adaptation and regeneration. Mechanotransduction pathways are of great interest in elucidating how mechanical signals produce such observed effects, including reduced tissue mass loss, increased healing and formation, and cell differentiation. While mechanobiology in the adaptation of cells and tissues is observed and recorded in the literature, its application in disease mechanism and treatment is under development. We would congratulate the opening of the Mechanobiology in Medicine journal, which provides an effective platform for advanced research in basic mechanotransduction and its translation in disease diagnosis, therapeutics, and beyond. This review aims to develop a cellular and molecular understanding of the mechanotransduction processes in tissue regeneration, which may provide new insights into disease mechanisms and the promotion of healing. Particular attention is allotted to the responses of mechanical loading, including potential cellular and molecular pathways, such as mechanotransduction associated with mechanotransduction pathways (e.g., Piezo ion channels and Wnt signaling), immune-response, neuron development, tissue adaptation and repair, and stem cell differentiation. Altogether, these discussed data highlight the complex yet highly coordinated mechanotransduction process in tissue regeneration.

1. Introduction

Mechanobiology biology and biomechanical signal transduction is a novel approach to regulate signaling pathways, cellular and tissue regeneration, and attenuate organ and tissue degeneration, whereas the understanding of specific cellular responses is critical to delineate the underlying mechanism. Mechanobiology is closely involved and plays significant role in human nature and development, influencing various aspects of human biology, behavior, and adaptation. Dynamic physical signals with optimized loading parameters, i.e., intensity, duration, frequency, and stimulation profiles, have been shown to have the potential to regulate tissue adaptation, such as in bone and cartilage. The pathways induced by loading are of great interest in elucidating how physical signals produce such observed effects, including increased/reduced stem cell activities, functional disuse-induced cellular loss, enhanced formation, and cell differentiation. In the musculoskeletal system alone, as an example, bone mineral density (BMD) and muscle strength are highly biomechanically related. High physical activity level has been associated with increased bone mass and low fracture risk and is recommended to reduce fractures in old age [16,17,39,40,56,61]. Understanding the mechanobiological aspects of human nature and development helps unravel the intricate connections between mechanical loading and human biology, which provides insights into the fundamental processes that shape human growth, behavior, and overall well-being. Moreover, incorporating mechanobiological principles into various fields, such as medicine, rehabilitation, sports, physical therapy, and psychology, can contribute to developing effective interventions and strategies for human development and optimal functioning. Some primarily interested and impacted areas where mechanobiology intersects with human nature and development are discussed in this review.

2. Mechanobiology in various biological systems

2.1. Skeletal and muscle growth and remodeling

Mechanical forces are crucial for skeletal growth and bone remodeling throughout life [6,22,35,36,43]. Weight-bearing activities and mechanical loading stimulate bone formation and density [32,50] embryonic. Forces exerted on bones during physical activity induce cellular responses in various bone cells, such as osteoblasts, osteoclasts, and osteocytes, regulating bone remodeling and adaptation. In the clinic, these data help promote skeletal health, prevent osteoporosis and joint degeneration, and develop strategies for tissue regeneration.

It is observed that functional disuse can induce bone loss and muscle atrophy. The most immediate and significant are the musculoskeletal implications in bone and muscles [13,19,37,47,54]. Results of the effect of microgravity on bone tissue from 4.5- to 14.5-month-long missions demonstrated that bone mineral density (BMD, g/cm^2) and mineral content (BMC, g) are decayed in the whole body of the astronauts [38]. The greatest BMD losses have been observed in the skeleton of the lower body, i.e., in pelvic bones ($-11.99 \pm 1.22\%$) and the femoral neck ($-8.17 \pm 1.24\%$), while there was no evitable decay found in the skull region. Overall changes in bone mass of the whole skeleton of male cosmonauts during about 6 months on a mission made up $-1.41 \pm 0.41\%$ and suggest the mean balance of calcium over flight equal to $-227 \pm$

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62.8 mg/day. On average, the magnitude and rate of the loss are staggering; astronauts lose bone minerals in the lower appendicular skeleton at a rate approaching 2% per month with muscle atrophy [41]. The mechanism that explains muscle and bone decay in the function disuse environment is still unclear. In recent years, considerable attention has focused on identifying particular parameters and exercise paradigms to ameliorate the deficits of muscle atrophy and bone density. The underlying factor producing these changes may be primarily due to the fluid flow and circulations in both muscular and bone tissues.

The ability of musculoskeletal tissues to respond to changes in their functional milieu is one of the most intriguing aspects of such living tissue, and certainly contributes to its success as a structure. The ability of bone and muscle to rapidly accommodate changes in its functional environment ensures that sufficient skeletal mass is appropriately placed to withstand the rigors of functional activity, an attribute described as Wolff's Law [68]. This adaptive capability of musculoskeletal tissues suggests that biophysical stimuli may be able to provide a site-specific, exogenous treatment for controlling both bone mass and morphology. Absence of functional loading results in the loss of bone mass [53–55,59,68], while exercise or increased activity results in increased bone mass. Similarly, the increasing exercise of musculoskeletal tissues can significantly increase blood flow, oxygen, and the exchange of fluid in muscle. During muscle contraction, several mechanisms regulate blood flow to ensure a close coupling between muscle oxygen delivery and metabolic demand [29,30].

2.2. Embryonic development

Mechanobiology contributes to the development of various organ systems during embryogenesis. Mechanical forces guide tissue morphogenesis, including processes such as cell migration, tissue folding, and organ formation. Each organ is developed to a unique shape and architecture to support its function. Mechanical environment is closely involved in structural development and functions in embryo growth, folds, and connections. Recent data have shown that mechanical forces are essential in the nervous system development, in which the neural tube closure (NTC) is controlled by actomyosin force generation at the neural plate's apical surface towards NTC [1,2,18]. Tissue stiffness and viscoelasticity are also critical to the migratory patterns of the neural crest cells [1,3–5,18]. Mechanical loading helps to shape the developing human body, influencing the formation of organs, limbs, and other anatomical structures.

2.3. Tissue engineering, repair, and regeneration

Mechanobiology has a critical role in wound healing and tissue repair processes. Mechanical tension and compression, such as in the skin, influence cell behavior and the organization of cells within healing tissues. These forces guide processes such as cell migration, proliferation, and extracellular matrix remodeling, contributing to wound closure, scar formation, and tissue regeneration. In skeleton tissue engineering, the development of artificial scaffold could take advantage of the mechanotransduction phenomena to achieve its integrity and function, which can lead to tissue regeneration and healing. Mechanical signals delivered to bone cells, as an example, may be interfered with the scaffold deformation, and material and tissue strength. Fortunately, mechanotransduction can be used to control the proliferation and differentiation of bone cells [24,25,33,65]. Fluid flow has been proposed as an important mechanical aspect for developing bone scaffolds [12,23,25,33]. Studies using bioreactors have helped us understand the phenomena of mechanotransduction used in scaffold design and cellular proliferation. For example, rotating bioreactors, flow perfusion bioreactors, and other mechanical stimuli such as strain have been designed to increase mass transfer by inducing dynamic flow conditions in culture. These mechanical stimuli can create osteoinductive factors on mesenchymal stem cells by the generated fluid shear stress, and induce the osteogenic differentiation of mesenchymal stem cells [46]. Among all, mimicking the natural bone strain to favor osteogenesis is one of the most rational aims for scaffold development.

In cardiovascular tissue regeneration and repair, mechanotransduction is directly involved in biomimetic cues through the use of biomaterials, engineered scaffolds, and dynamic loading in tissue forming and regeneration. These processes with dynamic and micromechanical environments can enhance cell adhesion, differentiation, and healing. Engineered hydrogels might represent an alternative to drug delivery vehicles to treat cardiac disease. Engineered cardiac patches can be used as off-the-shelf products to mimic the native extra cellular matrix (ECM). Due to their tissue-like biological, chemical, and mechanical properties, hydrogels represent potential carriers to release drugs/miRNAs into cardiac tissue [63]. Hydrogels are 3D hydrophilic polymer networks with tunable, compliant, and biomimetic behavior well suited for drug delivery [34,63,64,67,74]. The functional capabilities of hydrogels respond to various environmental and physical stimulus, such as pH, temperature, enzyme activity, electric or magnetic field, and tissue composition, with changes in physical and chemical properties [63,64,67,74]. Moreover, these new materials with low substance viscosity and slow gelling properties enable catheter delivery without an invasive surgery intervention.

2.4. Sensory systems perception and response to loading

Sensory systems, such as touch, hearing, and proprioception, rely on mechanobiological processes. Detection of mechanical forces by the somatosensory system is performed by primary afferent neurons that project long axons to the skin and deeper body structures. Mechanoreceptors in the skin detect tactile stimuli, converting mechanical forces into electrical signals that are interpreted by the nervous system. Mechanoreceptors are distributed in a variety of the entire system throughout the body, including in the skin, tendons, muscles, joint capsules, and viscera. Proprioceptors monitor the position of joints, tension in tendons and ligaments, and the state of muscular contraction. In the auditory system, sound vibrations are converted into electrical signals by mechanosensitive hair cells in the inner ear [21,34,60,63,64,67,74]. Proprioception, the sense of body position and movement, relies on mechanosensitive receptors within muscles, tendons, and joints. Recently, primary cilia has been found to play crucial roles in sensing mechanical signals. A primary cilium is a mechano-sensory organelle that responds to mechanical stimuli in the micro-environment. A cilium is also a chemosensor that senses chemical signals surrounding a cell. The overall function of a cilium is therefore to act as a communication hub to transfer extracellular signals into intracellular responses, which may be closely related to other signaling pathways, such as Hedgehog, Wnt, PDGFR, TGF-β, mTOR, OFD1 autophagy, and G-protein-couped receptors (GPCR) associated signaling pathways [49,51].

Mechanobiology is also closely linked to motor development and movement in humans. As infants grow, they experience changes in muscle tone, joint flexibility, and strength, which are influenced by mechanical cues. The interaction between sensory feedback and mechanical forces allows for development coordinated movements, balance, and motor skills. In the zebrafish studies, a common model for mechanobiology, when the Rohon-Beard (RB) neurons are stimulated, intraspinal reflex circuits are activated; then sensory-motor coordinates and adapts the mechanical environment [66]. The RB neurons sense the motor positions and discriminate anterior–posterior axis differences, which regulates the turning strength for appropriate escape behavior. Motor learning and refinement of movement patterns also involve the integration of mechanical feedback.

2.5. Neuron-response to mechanotransduction

Recently, the interrelation between mechanotransduction and pathological changes occurred during Alzheimer's disease (AD) progression.

Mechanotransduction is the process that converts mechanical stimuli from the ECM into biochemical signals inside the cell, with consequences on cell structure, gene expression, and physiological functions. The ECM-cytoskeleton link is further strengthened by enhancing Ca^{++} exchange through cell membranes, and by the presence of other critical cytosolic proteins, such as talin and vinculin [11,62], which interact with F-actin microfilaments and support the cell structure. Such Ca^{++} exchange and F-actin microfilaments can be regulated by external mechanical force [11]. A recent study has reported that external magnetic field (MF) stimulation with nerve growth factor functionalized superparamagnetic iron oxide-gold (NGF-SPIO-Au) nanoparticles (NPs) can induce Ca^{2+} influx, membrane depolarization, and enhance neuron differentiation [15]. The results indicated that total intracellular Ca^{2+} influx of neuron stem cells, PC-12, was improved by 300% and 535% by the stimulation of dynamic MF (1 Hz, 0.5 T, 30min) with NPs compared to dynamic MF alone and static MF with NPs, respectively, which was attributed to successive membrane depolarization. Dynamic MF upregulated both the neural differentiation marker (β3-tubulin) and the cell adhesive molecule (integrin-β1) with the existence of NPs, while static MF did not show these effects. The results suggested that dynamic loading by the magnetic field can regulate intracellular Ca^{2+} influx and enhance neuron differentiation and neuroregeneration rate [15].

2.6. Mechanobiology in immune response

It has been shown that macrophages play vital roles in tissue development, homeostasis, and repair, which dominate the progression of many inflammatory diseases. Mechanobiology is one of the critical factors in macrophage signaling, transcriptomics, and proteomics, under physiological and pathological conditions. However, the role of mechanobiology in macrophages needs to be better understood. The detailed mechanisms that tune circulating monocytes/macrophages and tissue-resident macrophage polarization, differentiation, specification, and functional plasticity remain elusive. At least, current literature results suggested that physical microenvironment factors influence M1 and M2 macrophage polarization. Under in vitro conditions, substrate stiffness regulates the phagocytic potential of macrophages [27,69]. Interstitial fluid enhances the polarization of macrophages toward the M2-like phenotype. The integrated response of immune cells with their microenvironments ultimately defines whether functional healing can occur or whether a wound never heals or is contracted into fibrotic pathological tissue [27].

2.7. Cellular and molecular pathways in response to mechanical loading

Bone remodeling involves all related cell types, i.e., osteoblast, osteoclast, osteocyte, T-cells, B-cells, megakaryocyte, and lining cells. Thus, all these cells are potentially mechano-sensitive and even interrelated. These cells respond to mechanical loading, and can express specific molecular pathways. Related molecular and gene factors are represented in this temporal sequence (Fig. 1). In response to mechanical loading, the first stage of remodeling reflects the detection of initiating triggering signals such as fluid flow and any other physical stimulation, e.g., pressure, electrical, and acoustic waves. Prior to activation, the resting bone surface is covered with bone-lining cells, including preosteoblasts intercalated with osteomacs. B-cells are present in the bone marrow and secrete osteoprotegerin (OPG), which suppresses osteoclastogenesis.

During the *Activation* phase, the endocrine bone-remodeling signal parathyroid hormone (PTH) binds to the PTH receptor on preosteoblasts. Damage to the mineralized bone matrix results in localized osteocyte apoptosis, reducing the local transforming growth factor β (TGF-β) concentration and its inhibition of osteoclastogenesis. In the *resorption* phase, in response to PTH signaling, MCP-1 is released from osteoblasts and recruits preosteoclasts to the bone surface. Additionally, osteoblast expression of OPG is decreased, and the production of CSF-1 and RANKL is increased to promote the proliferation of osteoclast precursors and differentiation of mature osteoclasts. Mature osteoclasts anchor to RGD-binding sites, creating a localized microenvironment (sealed zone) that facilitates the degradation of the mineralized bone matrix. In the *resorption* phase, in response to PTH signaling, MCP-1 is released from osteoblasts and recruits preosteoclasts to the bone surface. Additionally, osteoblast expression of OPG is decreased, and the production of CSF-1 and RANKL is increased to promote the proliferation of osteoclast precursors and differentiation of mature osteoclasts.

During the *Formation* phase, formation signals and molecules arise from the degraded bone matrix, mature osteoclasts, and potentially reversal cells. PTH and mechanical activation of osteocytes reduce sclerostin expression, allowing for Wnt-directed bone formation to occur.

Finally, in the *Termination* phase, sclerostin expression likely returns, and bone formation ceases. The newly deposited osteoid is mineralized, the bone surfaces return to a resting state with bone-lining cells intercalated with osteomacs, and the remodeling cycle concludes.

Mechanical stimulation is likely involved in each of these phases and eventually regulates related molecular and genetic factors. This unique spatial and temporal arrangement of cells within the BMU is critical to bone remodeling, ensuring coordination of the distinct and sequential phases of this process, such as activation, resorption, reversal, formation, and termination.

2.8. Osteocyte and its response to mechanical signals coupled with Wnt signaling

Osteocytes, cells embedded within the mineralized matrix of bone, are becoming the target of intensive investigation [7,8,57]. Osteoblasts are defined as cells that make bone matrix, and are thought to translate mechanical loading into biochemical signals that affect bone modeling and remodeling. The interrelationship between osteoblasts and osteocytes would be expected to have the same lineage, yet these cells also have distinct differences, particularly in their responses to mechanical loading and utilization of the various biochemical pathways to accomplish their respective functions. Among many factors, Wnt/β-catenin signaling pathway may be recognized as an essential regulator of bone mass and bone cell functions [8,57]. While osteocytes are embedded within the mineral matrix, Wnt/β-catenin signaling pathway may serve as a transmitter to transfer mechanical signals sensed by osteocytes to the surface of bone. Further, new data suggest that the Wnt/β-catenin pathway in osteocytes may be triggered by crosstalk with the prostaglandin pathway in response to loading which then leads to a decrease in expression of negative regulators of the pathway such as Sclerostin (Sost) and Dickkopf-related protein 1 (Dkk-1) [7,57]. Fig. 2 indicates the potential pathway in response to mechanical loading.

Sclerostin has been shown to be made by mature osteocytes and inhibits Wnt/β-catenin signaling by binding to LRP5 and preventing the binding of Wnt. Dkk-1 is highly expressed in osteocytes [31]. Clinical trial studies using antibodies to sclerostin have also been shown to increase bone mass, suggesting that targeting these negative regulators of Wnt/β-catenin signaling pathway might be anabolic treatments for diseases such as osteoporosis. Finally, mechanical loading has been shown to reduce sclerostin levels in bone [31,71,72], suggesting that one of the targets of the pathways, activated by the early events after mechanical loading, are the genes encoding these negative modulators of the Wnt/β-catenin signaling pathway.

There is still much to be learned regarding how the bone cells, i.e., osteocytes, sense and transmit signals in response to or absence of loading and further elevate the activity of other cells. Although fluid shear stress is proposed as a triggering force, the identity of these particular mechanical signals is still challenging to study. The osteocyte joins the osteoblast and osteoclast as targets for therapeutics to treat or prevent bone disease. Clearly targeting the Wnt/β-catenin pathway in osteocytes because of its central role in bone mass regulation and bone formation in response to mechanical loading may prove useful for designing new paradigms and pharmaceuticals to treat bone disease in the future.

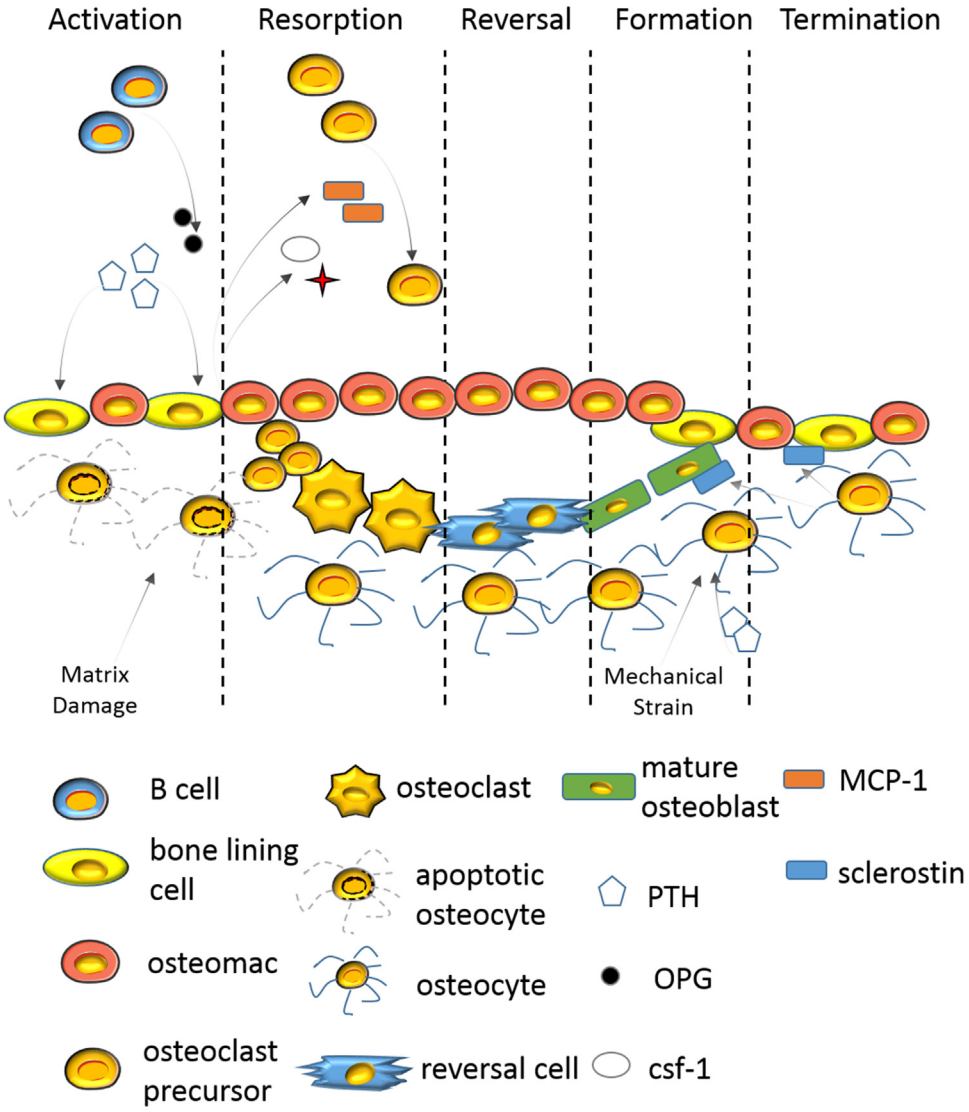

Fig. 1. Bone remodeling and its associated molecular pathways [57].

2.9. MicroRNA and its role in mechanotransduction in tissue regeneration

The newly discovered MicroRNAs (miRNAs) are short noncoding RNAs, which can be complementary to messenger RNA (mRNA) sequences to silence gene expression by either degradation or inhibitory translation of target transcripts [45]. Regulation of Runx2, bone morphogenic protein (BMP), and Wnt signaling pathways are the most well-studied miRNA-related osteoblast function. Positive and negative regulations of miRNAs on Runx2 expression have been shown to affect skeletal morphogenesis and osteoblastogenesis. Inhibition of osteoblastogenesis can result from miRNA-135 and miRNA−26a regulated BMP-2/Smad signaling pathway. Activation of Wnt signaling through miRNA-29a-targeted Wnt inhibitors is upregulated during osteoblast differentiation. Recent research has gained interest in studying the transcription and microRNA regulation better to understand gene expression regulation in a mechanical loading model. Transcription factors can bind to motifs in the promoter of genes and directly affect their expression. Therefore, mechanotransduction in bone may result in transcription factors alteration for regulation.

2.10. Piezo 1/2 in mechanosensory transduction

The role of mechanotransduction in regulating cells and tissues is recognized by several cellular and molecular pathways, among which Piezo 1 and Piezo 2 ion channels significantly impact the mechanosensory mechanism. The 2021 Nobel Prize awarded for discovering the Piezo1 and Piezo2 mechanoreceptors marks a milestone for the mechanobiology field by recognizing the essential role mechanical force plays in all its manifestations for living organisms. This shines a spotlight on the role mechanoreceptors play in the sustainability of different life forms, in a variety of environments, including microgravity for human colonization of outer space. Mechanosensitive Piezo ion channels, including Piezo1 and Piezo2, are evolutionarily conserved proteins; and they are critical for normal physiological processes in mammals [9,10,48]. Piezo1 is localized at or near the plasma membrane. Ge J et al. have explored the structure of Piezo1 using a single-particle cryo-electron microscopy, and they found that Piezo1 formed a trimeric propeller-shaped structure, including three blades, a central cap, and core transmembrane segments [14,75]. Besides, its characteristically curved blades and the core transmembrane segments

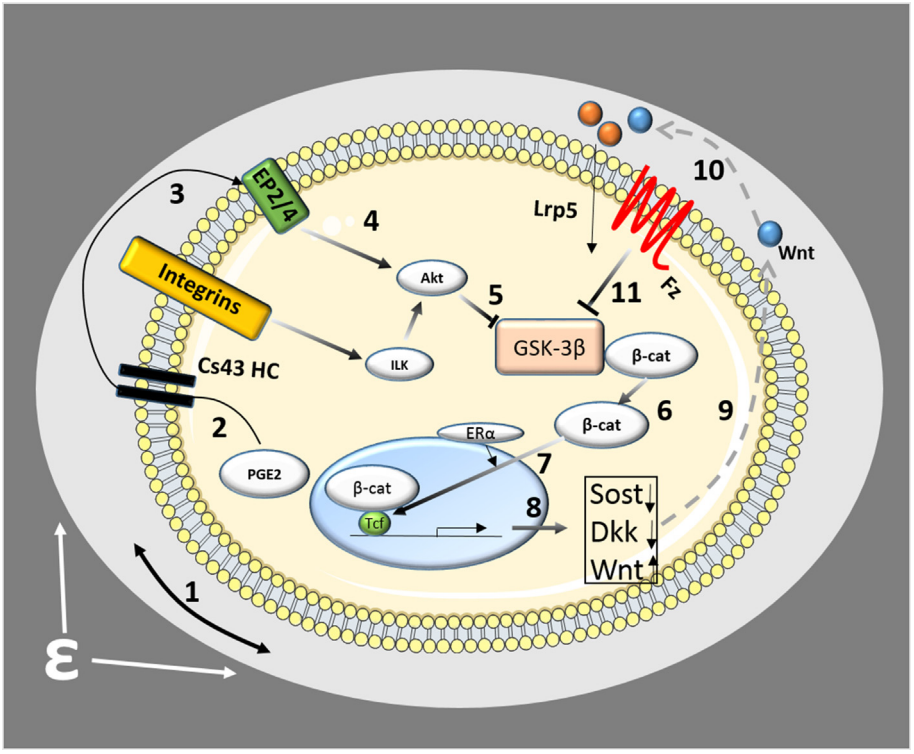

Fig. 2. Mechanical loading, e.g., fluid shear stress, induced Wnt signaling activation [7]. The osteocyte perceives mechanical load applied to bone (ε) through an unknown mechanism, although fluid flow generated through the lacunar-canalicular system may be a critical component of this perception, 'step **1**'. Perception of load (strain) triggers a number of intracellular responses including the release of PGE2, '**2**' through a poorly understood mechanism into the lacunar-canalicular fluid where it can act in an autocrine and paracrine fashion. Connexin-43 hemichannels (CX43 HC) in this PGE2 and integrin proteins appear to be involved. The binding of PGE2 to its EP2 and EP4 receptor, '**3**', leads to a downstream inhibition of GSK-3β, '**5**' (likely mediated by Akt, '**4**') and the intracellular accumulation of free β-catenin, '**6**'. (Integrin activation can also lead to Akt activation and GSK-3β inhibition.) New evidence suggests that ER may participate in the nuclear translocation of β-catenin, '**7**' which leads to changes in the expression of a number of key target genes '**8**'. One of the apparent consequences is the reduction in sclerostin and Dkk1, '**9**' with increased expression of Wnt, '**10**' (which one or ones is unknown). The net result of these changes is to create a permissive environment for the binding of Wnt to Lrp5-Fz and amplification of the load signal, '**11**'.

(central cation-selective pore) as a pivot have formed a lever like an apparatus. This lever-like mechanotransduction mechanism might enable Piezo1 channels to allow cation-selective translocation. In cells, Piezo1 channels can respond rapidly to diverse forms of mechanical stimulations and convert mechanical cues into biochemical signals to modulate various physiological processes. In our recent study, it has been demonstrated that Piezo1 can transduce dynamic mechanical loading induced by local ultrasound stimulation into intracellular Ca^{2+}, and the Ca^{2+} acted as a second messenger to activate ERK1/2 phosphorylation and perinuclear F-actin polymerization in bone-like cells [73]. The results indicate Piezo1 as a potential novel therapeutic target for fracture healing. In the cardiovascular adaptation, it has been shown that Piezo1 channels as sensors of frictional force (shear stress) and determinants of vascular structure in both development and adult physiology [44,58]. Global or endothelial-specific disruption of mouse Piezo1 profoundly disturbed the developing vasculature and was embryonic lethal within days of the heart beating [44,58]. Piezo-mediated mechanobiology is found significant in brain and central nerve system. Piezo-type mechanosensitive ion channel component 1 (Piezo1), a protein found in metazoans, is highly expressed in the brain and involved in sensing changes in the mechanical microenvironment. It has been shown that Piezo1-mediated mechanotransduction is closely related to glial cell activation and neuronal function [76]. Piezo-1 has been demonstrated to promote cell metastasis and invasion in various cancers, such as melanoma [26,52], prostate cancer [20], breast cancer [42,70], and osteosarcoma [28].

3. Future directions

The effects of mechanobiology may be one of the most intriguing aspects of living tissue, which have harnessed in such a way that physical regulation and stimulation can act as a mechanobiological mediator in various cells, tissues, and organs scaffold to regulate cellular and tissue regeneration and proliferation. Such signals must be performed and conducted in a dynamic manner, and potentially served as a non-invasive approach. Strong evidences have shown that mechanotransuduction plays critical roles in cell–cell communication, normal and disease adaptation and progress, embryonic development, tissue homeostasis, tissue engineering and regeneration, and immune response and tumor therapy. However, the fundamental mechanisms of mechanotransduction remain unclear, thus prevent of clinical applications. The future direction of research is likely to involve molecular and generic mechanisms, enhance our knowledge to develop novel treatment and technology, and explore drug delivery and clinical applications. These are the goals and scopes of the MBM Journal. Future development of mechanobiology with advanced topics is promising, at least, including the following areas, 1) mechanotransduction in tissue and engineered constructs for regeneration, 2) unraveling of molecular and genetic mechanisms, 3) genetic pathways and integration of omics technologies, 4) engineered biomaterials, 5) immunology and cancer, 6) synthetic biology approach development and single-cell and RNA-seq technologies, and 7) clinical translation and applications. Further understanding of cell-cell and cell-tissue communication and sensing of mechanical cues will have great potential to develop new novel interventions for various diseases and advance our understanding of regenerative medicine and therapies.

Ethical statement

This review does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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