Piezo1 and Bone Health: A Survey on Mechanotransduction and Its Implications for Osteoarthritis and Osteoporosis

Abstract

Piezo1, a mechanosensitive ion channel, is pivotal in mechanotransduction, the process converting mechanical stimuli into cellular responses, significantly impacting bone remodeling. This survey explores Piezo1's role in maintaining bone integrity and its potential therapeutic implications for conditions like osteoarthritis and osteoporosis. Recent studies reveal Piezo1's activation by mechanical forces, underscoring its importance in bone health. Piezo1 modulates cellular activities, influencing osteoblast and osteoclast dynamics, crucial for bone adaptation. Its mechanosensitive properties facilitate the conversion of mechanical stretch into biochemical signals, essential for cellular responses and bone homeostasis. In osteoarthritis, Piezo1 affects chondrocyte behavior, contributing to cartilage degradation, while in osteoporosis, it plays a role in bone density regulation, offering potential as a therapeutic target. The survey highlights the integration of Piezo1-targeted therapies with bio-inspired materials, enhancing regenerative medicine approaches for bone repair. Future research should focus on elucidating Piezo1's activation mechanisms and interactions with cellular components to develop targeted interventions, improving outcomes in osteodegenerative diseases. By advancing our understanding of Piezo1's mechanotransductive functions, this survey provides a foundation for innovative therapeutic strategies in bone health.

1 Introduction

1.1 Introduction to Piezo1 and Mechanotransduction

Piezo1 is a mechanosensitive ion channel essential for mechanotransduction, which converts mechanical stimuli into biochemical signals within cells. It is crucial for various cellular functions, including the maintenance of homeostasis and the regulation of bone remodeling, where mechanical forces influence the activity of osteoblasts, osteoclasts, and osteocytes [1]. The activation of Piezo1 in response to mechanical stimuli underscores its importance in bone health, contributing to structural integrity and function [2].

The distribution of Piezo1 within live cells is affected by membrane curvature, which plays a significant role in biological processes such as cytokinesis, cell migration, and wound healing [3]. Understanding the modulation of Piezo1 function is vital for elucidating its physiological roles and activation mechanisms [4]. Furthermore, research into the control of Piezo1 channels, which are large, mechanically activated ion channels, remains critical [5].

Beyond bone tissue, Piezo1 mediates mechanotransduction in various cellular activities, including membrane deformation [6]. Mechanical stretch activates Piezo1, influencing cellular responses such as division and apoptosis in epithelial cells [7]. Investigating how Piezo1 mediates these responses is essential for advancing knowledge of bone development and repair, addressing existing gaps in the field.

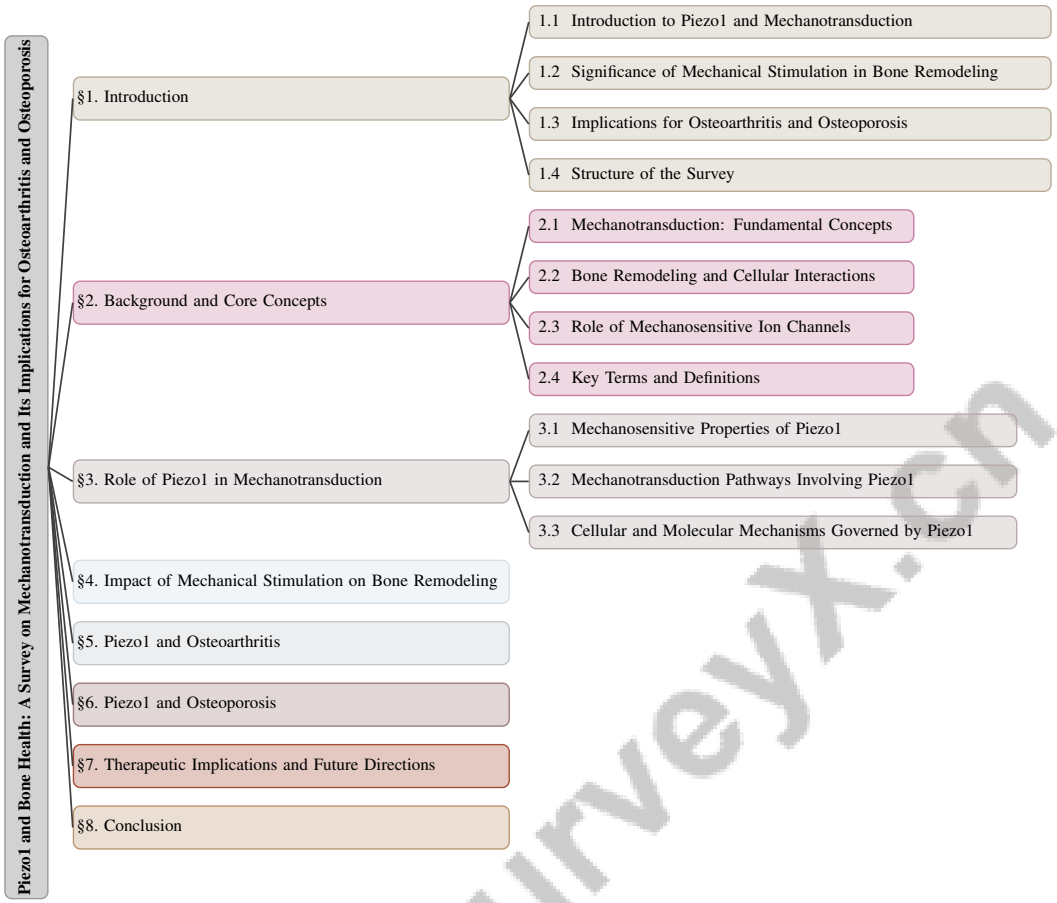


Figure 1: chapter structure

1.2 Significance of Mechanical Stimulation in Bone Remodeling

Mechanical stimulation is fundamental to bone remodeling, serving as a critical determinant of bone homeostasis and influencing the balance between osteoblast and osteoclast activity [8]. The mechanostat theory posits that bone tissues adapt to their mechanical environment, underscoring the role of mechanical forces in maintaining bone integrity and health [8]. Mechanical strain acts as a primary stimulus for bone adaptation, where mechanical and biological signals converge to regulate the remodeling process [9]. This interaction is vital for effective tissue adaptation and long-term bone health, as mechanical forces facilitate the transport of nutrients and signaling molecules necessary for bone growth under static loads [10].

The cellular response to mechanical stimuli involves complex interactions with the extracellular matrix (ECM), focal adhesions, and the cytoskeleton, which are integral to mechanotransduction [11]. This network is crucial for converting mechanical signals into biochemical responses, thus regulating cellular behavior and bone tissue dynamics. Mechanical loading activates Piezo1 ion channels in osteocytes, which sense mechanical signals and play a significant role in the mechanotransductive process [12]. The importance of mechanotransduction in osteocytes is emphasized as a vital component of bone remodeling and adaptation to mechanical stimuli [13].

Recent advancements in multiscale modeling highlight the need to integrate interactions across different scales, from molecular to macroscopic levels, to accurately capture the complex mechanical behaviors of bone [14]. These models are essential for understanding the distinct responses of cortical and trabecular bone to mechanical stimuli, given their unique structural properties [14]. Additionally, mechanical load and oxygen levels are critical for cellular metabolism and function [15]. The absence of mechanical forces can lead to conditions like disuse osteoporosis, illustrating their essential role in bone homeostasis [16].

Despite the significance of mechanical stimuli in bone remodeling, current methodologies often struggle to apply controlled and localized forces at multiple points on the cell membrane, which is necessary for accurately mimicking natural signaling pathways [17]. This challenge is further complicated in scaffold-based tissue engineering therapies, which aim to replicate the complex mechanical environment required for effective tissue repair [18]. Future research should focus on developing advanced methodologies to simulate and apply mechanical stimuli accurately, enhancing our understanding of bone mechanobiology and improving therapeutic interventions.

1.3 Implications for Osteoarthritis and Osteoporosis

Piezo1's involvement in mechanotransduction pathways is crucial for understanding its implications in osteodegenerative diseases such as osteoarthritis and osteoporosis. In osteoporosis, characterized by disrupted bone remodeling dynamics, Piezo1 is vital for maintaining bone mass and strength, positioning it as a potential therapeutic target to mitigate bone loss. The mechanical properties of bone, which deteriorate with age and disease, are significantly influenced by Piezo1, affecting individuals' quality of life. The ratio Γ has been proposed as a non-invasive diagnostic tool for assessing bone strength, potentially enhancing osteoporosis management by highlighting Piezo1's mechanical contributions [19]. Furthermore, the nonlinear response of disordered elastic networks serves as a surrogate for evaluating bone strength, underscoring Piezo1's potential in identifying osteoporotic characteristics [19].

In osteoarthritis, Piezo1's role in chondrocytes significantly influences endochondral ossification and disease progression [20]. The mechanosignaling pathways mediated by Piezo1 in cartilage health are crucial for understanding how mechanical stimuli contribute to osteoarthritis and for identifying therapeutic targets [21]. Although activating Piezo1 channels through non-mechanical means poses challenges, limiting the study of their functions in chronic inflammatory diseases, dietary strategies have been shown to modulate Piezo1's mechanical response, offering insights into managing Piezo1-related pathologies [3]. Mechanical stretch activates Piezo1, stimulating cell division in low-density regions, which is crucial for maintaining homeostasis and further emphasizing its role in osteoarthritis [7]. Addressing these challenges is essential for advancing our understanding of Piezo1's physiological roles and developing novel therapeutic strategies for osteodegenerative diseases.

1.4 Structure of the Survey

This survey is structured to provide a comprehensive understanding of Piezo1's role in mechanotransduction and its implications for bone health, particularly concerning osteoarthritis and osteoporosis. The survey begins with an **Introduction** section, introducing Piezo1 as a mechanosensitive ion channel pivotal in mechanotransduction and setting the stage for its significance in bone remodeling and potential impact on osteodegenerative conditions.

Following the introduction, the **Background and Core Concepts** section delves into fundamental concepts of mechanotransduction, bone remodeling, and the function of mechanosensitive ion channels, with a focus on Piezo1. This section aims to establish a foundational understanding necessary for comprehending subsequent discussions.

The **Role of Piezo1 in Mechanotransduction** section explores how Piezo1 translates mechanical stimuli into cellular responses, detailing its mechanosensitive properties and the pathways it influences. This is followed by an in-depth analysis of cellular and molecular mechanisms governed by Piezo1 activation.

In the **Impact of Mechanical Stimulation on Bone Remodeling** section, the survey examines how mechanical forces mediated by Piezo1 influence bone remodeling processes, emphasizing the dynamics of osteoblasts and osteoclasts.

The survey then transitions to disease-specific discussions, with sections on **Piezo1 and Osteoarthritis** and **Piezo1 and Osteoporosis**. These sections explore the mechanotransduction pathways involving Piezo1 that contribute to these conditions, its impact on cartilage health, inflammatory responses, and bone density regulation.

Finally, the survey concludes with a section on **Therapeutic Implications and Future Directions**, discussing potential therapeutic strategies targeting Piezo1, challenges in bone mechanobiology, and

the development of bio-inspired materials for regenerative medicine. This structure ensures a logical progression from fundamental concepts to applied implications, providing a holistic view of Piezo1's role in bone health.The following sections are organized as shown in Figure 1.

2 Background and Core Concepts

2.1 Mechanotransduction: Fundamental Concepts

Mechanotransduction is a pivotal biological process where cells convert mechanical stimuli into biochemical signals, crucial for physiological functions like bone remodeling. This capacity to sense mechanical cues is essential for cellular function and homeostasis, especially in mechanically active tissues [5]. The mechanostat theory posits that bone adapts to mechanical environments but overlooks the dynamic nature of the osteocyte lacunocanalicular network (OLCN) and its influence on bone's mechanical state [13]. Understanding mechanotransduction requires exploring the interplay between mechanical loads, biochemical signals, and cellular activities [16].

Recent advancements, such as engineered systems for precise mechanical stimuli application, have enhanced mechanotransduction exploration [22]. Proteins like Piezo1 are key mechanosensors, converting mechanical stretch into cellular responses, illustrating mechanotransduction's core principles [7, 5]. The mechanical behavior of bone, influenced by density, porosity, and material quality, complicates understanding bone fragility and conditions like osteoporosis [16]. Advanced models are necessary to simulate bone's mechanical behavior under stress, highlighting mechanotransduction's role in maintaining tissue integrity [13]. Understanding cellular interpretation of mechanical signals is vital for elucidating physiological processes and disease mechanisms [22].

2.2 Bone Remodeling and Cellular Interactions

Bone remodeling is a dynamic process involving osteoblasts, osteoclasts, and osteocytes, ensuring skeletal integrity. Mechanical loading regulates fluid flow and shear stresses that stimulate osteocytes, key mechanosensors coordinating remodeling through signaling to osteoblasts and osteoclasts [16, 13]. Osteoblasts and osteoclasts interact within Bone Multicellular Units (BMUs) to balance bone formation and resorption, crucial for skeletal functionality [23]. This balance is influenced by spatial dynamics and hormonal factors like parathyroid hormone [24, 25].

The Mechanical Regulation of Cell Differentiation Model (MRCDM) captures tissue property changes due to mechanical loading, providing insights into bone remodeling's dynamic nature [1]. However, current methods struggle with bone remodeling's complexities, particularly rapid bone mineral density changes [1]. Osteoblast differentiation involves stages regulated by signaling pathways, with mechanosignaling processes like integrin-mediated signaling playing integral roles [13]. Understanding these interactions is crucial for developing therapeutic strategies for bone-related diseases [23].

2.3 Role of Mechanosensitive Ion Channels

Mechanosensitive ion channels are critical components converting mechanical stimuli into biochemical signals. Piezo1, significant for mediating stretch-activated currents in osteocytes and osteoblasts, plays a crucial role in bone anabolism [26]. Functioning under the force-from-lipid paradigm, Piezo1 opens in response to lipid bilayer deformations, acting as a mechanosensor [26]. The interaction between Piezo1 and the cytoskeleton is essential for its function, with cytoskeletal elements affecting Piezo1's mechanical force response [27].

Piezo1's ability to mediate distinct cellular responses based on mechanical stimuli underscores its versatility in mechanotransduction [7]. This adaptability is crucial for cellular homeostasis in varying mechanical environments. Challenges in existing models often arise from simplified assumptions about signal transduction [27]. Innovative approaches like agent-based models simulate mechanotransduction pathways, enhancing understanding of molecular interactions [28]. Additionally, a light-gated PIEZO1 channel using an azobenzene-based photoswitch provides new avenues for studying Piezo1 activity [29].

2.4 Key Terms and Definitions

This survey emphasizes key terms crucial for understanding mechanotransduction and bone health, focusing on bone remodeling, osteoblast and osteoclast roles, and mechanical loading's impact [16, 28, 30, 31].

Mechanotransduction refers to converting mechanical stimuli into biochemical signals, mediated by mechanosensitive ion channels like Piezo1 and Piezo2, which have distinct roles across tissues [4]. The survey categorizes research into channel families, including PIEZO, OSCA/TMEM63, K2P, and TRP, highlighting mechanosensation roles in processes like touch and blood pressure sensing [5].

Bone Remodeling involves the balanced activities of osteoblasts and osteoclasts, characterized by resorption, formation, and quiescence phases [25]. Relying solely on Bone Mineral Density (BMD) poses challenges, as it overlooks factors affecting bone strength, such as architectural quality [19].

Osteoarthritis is marked by cartilage and bone deterioration. Mechanotransduction pathways involving TRPV4 and PIEZO1 channels regulate chondrocyte responses to mechanical stress, influencing cartilage integrity [32, 21]. Disruption of these pathways can contribute to osteoarthritis development.

Osteoporosis is characterized by reduced bone density and fracture risk, often from imbalances in remodeling. Traditional BMD assessment is being reevaluated in favor of approaches considering stress backbone and mechanical properties [19].

Understanding the terminology and interrelationships among bone mechanical properties, osteocyte roles, and bone development processes is essential for advancing bone health research and formulating effective therapeutic strategies. This knowledge aids in elucidating how mechanical forces influence remodeling and adaptation, informing targeted interventions to enhance bone quality and reduce fracture risk [27, 30, 33, 16]. Challenges include current diagnostic tools' limitations and the need for comprehensive models capturing bone biology's dynamic nature.

3 Role of Piezo1 in Mechanotransduction

Category	Feature	Method
Mechanosensitive Properties of Piezo1	Mechanotransduction Mechanisms	SEGM[25], SACD-Piezo1[7]
Mechanotransduction Pathways Involving Piezo1	Structural and Functional Analysis	HPA[4]
Cellular and Molecular Mechanisms Governed by Piezo1	Optogenetic Techniques	mOP1[29]

Table 1: Summary of methods used to investigate the mechanosensitive properties, mechanotransduction pathways, and cellular mechanisms involving Piezo1. This table categorizes the approaches into mechanotransduction mechanisms, structural and functional analysis, and optogenetic techniques, highlighting the diverse methodologies employed in the study of Piezo1.

Piezo1, a mechanosensitive ion channel, is pivotal in converting mechanical stimuli into biochemical signals, impacting cellular behaviors and physiological processes. Table 1 provides an overview of the various methods employed to study the mechanosensitive properties of Piezo1, its role in mechanotransduction pathways, and the cellular and molecular mechanisms it governs. Additionally, Table 2 provides an overview of the diverse methods used to study the mechanosensitive properties of Piezo1, its involvement in mechanotransduction pathways, and the cellular and molecular mechanisms it influences. This section delves into Piezo1's mechanosensitive properties and its activation's implications for cellular function.

3.1 Mechanosensitive Properties of Piezo1

Piezo1 responds dynamically to mechanical forces like shear stress and tension, inducing conformational changes that facilitate ion influx [5]. This conversion of mechanical stretch into biochemical signals initiates key signaling pathways influencing cellular responses [7]. The force-from-lipid paradigm highlights Piezo1's activation by lipid bilayer tension, with cytoskeletal elements modulating its gating and sensitivity [6, 16]. Piezo1's spatial distribution, influenced by membrane curvature, underscores its mechanosensitive nature [22].

Piezo1's function is further shaped by tissue structural properties, affecting bone remodeling dynamics and cellular behavior near bifurcation points [25]. Bone's mechanical properties, such as density

and porosity, along with qualitative factors like collagen cross-linking, are critical for fracture susceptibility. Piezo1's mechanotransduction role in osteoblasts is vital for bone formation and maintenance, with its disruption leading to structural impairments, marking it as a therapeutic target for osteoporosis and related conditions [34, 30, 35, 12, 31].

3.2 Mechanotransduction Pathways Involving Piezo1

Piezo1 is integral to mechanotransduction pathways, converting mechanical stimuli into cellular responses essential for physiological processes. Membrane curvature regulates Piezo1's distribution and function, emphasizing its role in cellular homeostasis [36]. Piezo1-mediated pathways involve interactions with focal adhesions and cytoskeletal dynamics, highlighting its complexity in mechanotransduction [32, 11].

The discovery of an allosteric Yoda1 binding pocket in Piezo1 elucidates its activation under mechanical tension, advancing understanding of its signaling mechanisms [26]. Osteocytes employ Piezo1 among other mechanosensors to transduce mechanical signals, crucial for skeletal integrity [13]. Comparative analyses of Piezo1 and Piezo2 interaction with mechanical stimuli enhance the comprehension of their distinct mechanotransduction roles [4].

3.3 Cellular and Molecular Mechanisms Governed by Piezo1

Piezo1 activation regulates cellular mechanisms by transducing mechanical stimuli into biochemical signals, influencing bone remodeling. Increased intracellular calcium levels from Piezo1 activation initiate signaling cascades affecting proliferation, differentiation, and apoptosis [37]. Piezo1 modulates osteoblast-osteoclast interactions through mechanical and biochemical feedback, with multiscale models predicting bone volume changes [14, 38].

Nano-mechanical stimuli reveal significant changes in nuclear morphology, aligning with models of bone remodeling based on osteoclast and osteoblast dynamics [17, 39]. Piezo1's role in mechanotransductive processes affects osteoblast-osteoclast interaction stability, integrating biochemical, biomechanical, and geometrical regulations [40, 23, 24].

Figure 2 illustrates Piezo1's mechanotransduction role through three scientific analyses: the structural and functional analysis of Trans-Membrane Protein 1 in the heart, GPI-mCherry sorting in response to mechanical forces, and stress-induced unfolding of a protein leaflet, demonstrating Piezo1's impact on cellular architecture and function [29, 36, 26].

Feature	Mechanosensitive Properties of Piezo1	Mechanotransduction Pathways Involving Piezo1	Cellular and Molecular Mechanisms Governed by Piezo1
Activation Mechanism	Lipid Bilayer Tension	Allosteric Binding Pocket	Calcium Influx
Role in Cellular Function	Signal Pathway Initiation	Homeostasis Regulation	Affects Proliferation
Impact on Bone Remodeling	Influences Bone Density	Skeletal Integrity Maintenance	Volume Change Prediction

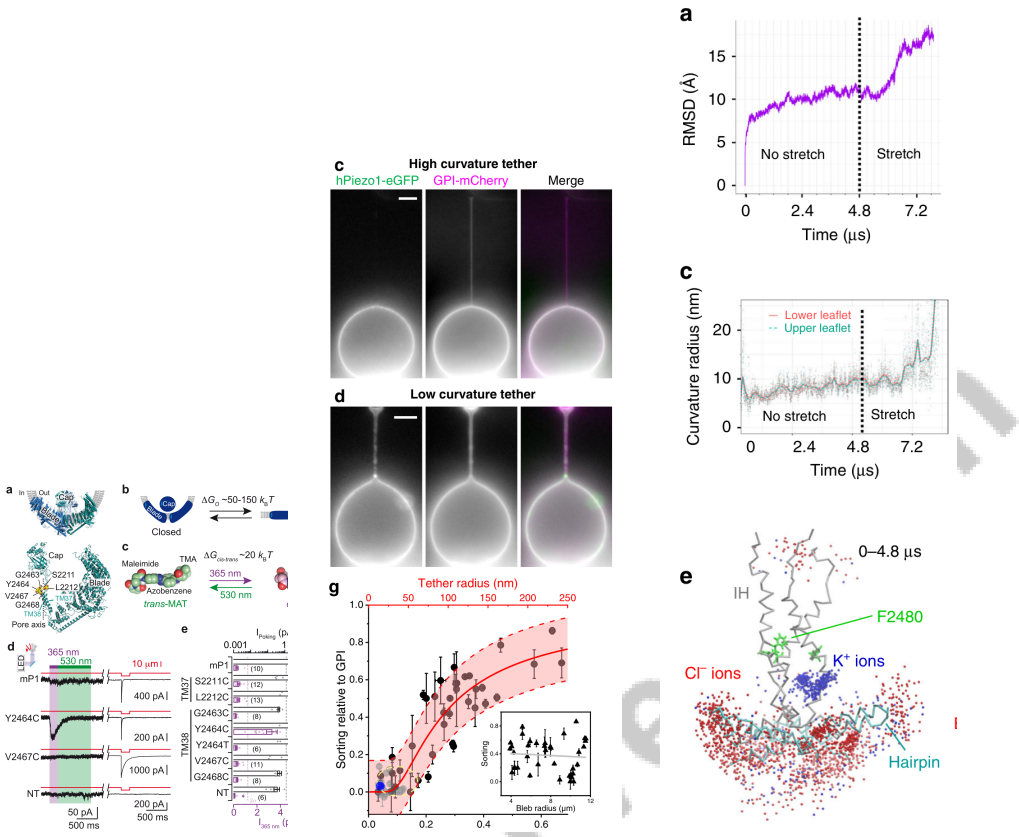
Table 2: This table provides a comprehensive comparison of the mechanosensitive properties, mechanotransduction pathways, and cellular and molecular mechanisms associated with the Piezo1 ion channel. It highlights the activation mechanisms, roles in cellular function, and impacts on bone remodeling, illustrating the multifaceted nature of Piezo1 in physiological processes.

4 Impact of Mechanical Stimulation on Bone Remodeling

The interaction between mechanical stimulation and bone remodeling is governed by complex cellular mechanisms, with Piezo1, a mechanosensitive ion channel, playing a pivotal role in mechanotransduction. Piezo1 activation is key to understanding how mechanical forces influence cellular behavior and bone health. The following subsection explores the activation of Piezo1 and its critical role in mediating cellular responses that drive bone remodeling.

4.1 Piezo1 Activation and Cellular Responses

Piezo1 is central to mechanotransduction, where mechanical stimuli trigger cellular responses crucial for bone remodeling and adaptation. Upon exposure to mechanical force, Piezo1 undergoes conformational changes that facilitate calcium ion influx, initiating signaling cascades that regulate cell proliferation, differentiation, and apoptosis, thereby influencing bone homeostasis and repair



(a) Structural and Functional Analysis of the Trans-Membrane Protein 1 (trans-MAT) in the Human Heart[29]

(b) Sorting of GPI-mCherry into blebs on tethered cells[36]

(c) Stress-induced unfolding of a protein leaflet in a membrane[26]

Figure 2: Examples of Cellular and Molecular Mechanisms Governed by Piezo1

[26, 12]. Beyond bone cells, Piezo1 in endothelial cells senses physical activity to regulate blood pressure, underscoring its broader physiological roles [2]. Additionally, mechanical stretch promotes epithelial cell division via Piezo1, highlighting its importance in mechanical stimulation contexts [7].

The mechanostat theory suggests that osteocytes establish a dynamic mechanical reference state evolving over time, emphasizing Piezo1's role in adapting to mechanical environments [27]. Advanced models like the Spatial Evolutionary Game Model elucidate the complex interactions and feedback mechanisms in bone remodeling, demonstrating how mechanical forces shape cellular responses [25]. Moreover, Piezo1 significantly influences stem cell behavior, where mechanical forces can enhance regenerative therapies [22]. However, the full spectrum of mechanosensitive channels and their interactions within cellular contexts remains incompletely understood, highlighting the need for further research [5].

4.2 Role of Mechanical Forces in Osteoblast and Osteoclast Dynamics

Mechanical forces are crucial in regulating the balance between osteoblast and osteoclast activities, essential for maintaining bone homeostasis and structural integrity. These stimuli modulate the functions and interactions of bone cells during remodeling. Osteoblasts, which facilitate bone formation, and osteoclasts, responsible for bone resorption, adjust their activity in response to mechanical loading, enabling bone adaptation to its mechanical environment [41].

Micromotion levels at the bone-implant interface significantly influence tissue volume and tissue-to-implant contact ratios, reflecting osteoblast and osteoclast activity during remodeling. Variations in

micromotion elicit differential cellular responses, impacting implant integration success and bone integrity maintenance [41]. Understanding the mechanical environment's effects on cellular dynamics is crucial for optimizing conditions to enhance bone healing and regeneration.

Current bone remodeling models often fail to capture the complexity of spatial interactions between osteoblasts and osteoclasts, which are vital for understanding physiological remodeling processes. This oversight hampers the accurate prediction of mechanical loading outcomes on bone tissue [25]. Advanced modeling approaches that integrate spatial and temporal factors are essential for comprehensively understanding how mechanical forces influence osteoblast and osteoclast dynamics, ultimately guiding the development of effective therapeutic strategies for bone-related disorders.

In recent studies, the role of Piezo1 in osteoarthritis has garnered significant attention due to its involvement in mechanotransduction pathways, which are critical for maintaining cartilage health and managing inflammatory responses. Figure 3 illustrates the hierarchical structure of Piezo1's role in osteoarthritis, emphasizing its central function in mechanotransduction. The figure highlights how Piezo1 influences both cartilage matrix synthesis and degradation, as well as its modulation of inflammatory responses. This comprehensive overview positions Piezo1 as a promising therapeutic target for the treatment of osteoarthritis, underscoring its potential to improve outcomes for affected individuals.

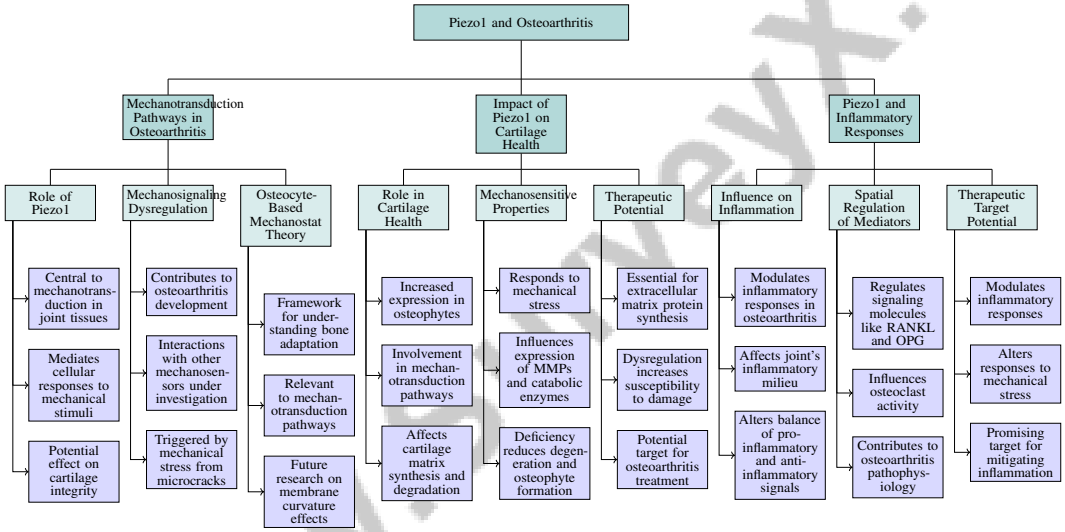


Figure 3: This figure illustrates the hierarchical structure of Piezo1's role in osteoarthritis, focusing on its impact on mechanotransduction pathways, cartilage health, and inflammatory responses. It highlights the central role of Piezo1 in mechanotransduction, its influence on cartilage matrix synthesis and degradation, and its modulation of inflammatory responses, positioning it as a potential therapeutic target for osteoarthritis treatment.

5 Piezo1 and Osteoarthritis

5.1 Mechanotransduction Pathways in Osteoarthritis

Piezo1 channels are central to mechanotransduction in joint tissues, significantly impacting osteoarthritis progression by mediating cellular responses to mechanical stimuli. The dysregulation of mechanosignaling pathways in chondrocytes can contribute to osteoarthritis development [32, 21]. The osteocyte lacunocanalicular network (OLCN) plays a crucial role in mechanotransduction, potentially affecting cartilage integrity in osteoarthritic conditions [27]. Piezo1's interactions with other mechanosensors in osteocytes are still under investigation [13]. Mechanical stress from microcracks in bone, common in osteoarthritic joints, may trigger Piezo1 activation, leading to osteocyte apoptosis and altered osteoblast activity, thereby exacerbating degenerative processes [42]. The osteocyte-based mechanostat theory provides a framework for understanding bone adaptation responses relevant to these pathways [8]. Future research should examine the effects of membrane curvature on Piezo1 distribution to further elucidate these pathways [36].

5.2 Impact of Piezo1 on Cartilage Health

Piezo1 is pivotal in maintaining cartilage health, with increased expression noted in human osteophytes, indicative of osteoarthritis [20]. This upregulation suggests Piezo1's involvement in mechanotransduction pathways that modify chondrocyte behavior and contribute to osteoarthritic cartilage changes. Activation of Piezo1 in chondrocytes affects signaling pathways that regulate cartilage matrix synthesis and degradation, potentially worsening degeneration. Its mechanosensitive properties enable responses to mechanical stress, influencing the expression of matrix metalloproteinases (MMPs) and catabolic enzymes responsible for cartilage degradation. Studies show that Piezo1 deficiency in chondrocytes reduces cartilage degeneration and osteophyte formation in animal models [31, 20]. Proper mechanotransduction is crucial for synthesizing extracellular matrix proteins that provide cartilage with load-bearing properties, and Piezo1 is essential in regulating these processes. Dysregulation in osteoarthritic cartilage disrupts these processes, increasing susceptibility to mechanical damage and joint degeneration, highlighting Piezo1 as a potential therapeutic target for osteoarthritis [32, 21, 31, 20]. Future research should explore Piezo1's influence on chondrocyte responses and potential interventions to mitigate its detrimental effects in osteoarthritic joints.

5.3 Piezo1 and Inflammatory Responses

Piezo1 plays a crucial role in modulating inflammatory responses in osteoarthritis, a condition marked by inflammation and cartilage degradation. Activation of Piezo1 channels affects the joint's inflammatory milieu, potentially influencing osteoarthritis progression [12]. The mechanotransduction pathways involving Piezo1 may alter the balance of pro-inflammatory and anti-inflammatory signals, impacting the inflammatory response of chondrocytes and other joint cells. The spatial distribution of signaling molecules such as RANKL and OPG is vital for regulating osteoclast activity, influencing the inflammatory environment in osteoarthritic joints [23]. Piezo1's modulation of these pathways suggests its role in the spatial regulation of inflammatory mediators, contributing to osteoarthritis pathophysiology. Recent studies emphasize Piezo1's potential as a therapeutic target in inflammatory diseases, highlighting its role in modulating inflammatory responses [43]. By influencing mechanotransductive pathways, Piezo1 may alter cellular responses to mechanical stress, a key factor in osteoarthritis-related inflammatory processes, positioning it as a promising pharmacological target for mitigating inflammation and improving joint health [44]. Future research should focus on elucidating the molecular pathways through which Piezo1 modulates inflammatory responses, particularly under mechanical stress, and assess its viability as a therapeutic target for alleviating osteoarthritis symptoms and progression [37, 12, 20]. Understanding these mechanisms could lead to innovative treatment strategies for chronic inflammatory diseases associated with joint degeneration.

6 Piezo1 and Osteoporosis

6.1 Piezo1's Role in Bone Density Regulation

Piezo1, a key mechanosensitive ion channel, is essential for bone density regulation, which is critical for maintaining skeletal integrity and preventing osteoporosis. It translates mechanical stimuli into biochemical signals that drive bone remodeling, thereby influencing bone density [45]. The architecture of the osteocyte lacunocanalicular network (OLCN) is crucial for understanding mechanical signal transmission within bone tissue, which is vital for regulating bone density [27]. Multiscale models that predict the effects of mechanical loading on bone health reveal how healthy and osteoporotic bones adapt differently to mechanical stimuli, underscoring Piezo1's mediating role [14, 46]. Cellular dynamics models further highlight Piezo1's critical role in maintaining optimal bone density by regulating bone remodeling [23]. Automated verification techniques enhance our understanding of temporal bone density changes, shedding light on Piezo1's contribution to bone health [47]. Additionally, nonlinear response methods quantitatively evaluate bone mechanical properties, clarifying Piezo1's role in bone density regulation [19].

6.2 Hormonal and Geometrical Regulation

Piezo1's regulation of bone density is closely linked to hormonal influences and the geometric characteristics of bone microstructure, which shape the mechanotransductive pathways governing bone remodeling. This illustrates the complex interactions among mechanical loading, osteoblast

and osteoclast cellular responses, and bone structural integrity. Alterations in Piezo1 function can significantly affect bone formation and resorption, highlighting its therapeutic potential for osteoporosis and disuse osteoporosis due to mechanical unloading [35, 12, 24, 16, 31]. Hormones such as parathyroid hormone and estrogen modulate osteoblast and osteoclast activity, influencing bone remodeling and density through mechanosensitive pathways, including those involving Piezo1. Geometric factors, particularly the structural properties of bone such as porosity and trabecular thickness, critically impact Piezo1's regulatory role in bone density. These properties affect the mechanical environment experienced by bone cells, modulating Piezo1 channel activation in response to mechanical deformations in the bone matrix. The introduction of the ratio Γ as a non-invasive diagnostic tool links bone strength to intrinsic properties, offering insights into the geometric contributions to mechanotransduction involving Piezo1 [19]. Understanding the interplay between hormonal signals and geometrical constraints is essential for comprehensively grasping Piezo1's regulation of bone density. These factors collectively influence the mechanical loading conditions that activate Piezo1, affecting downstream signaling pathways governing bone remodeling. Future research should focus on elucidating the specific mechanisms through which hormonal and geometrical factors influence Piezo1 activity, a key mechanotransducer in osteoblasts that mediates bone formation in response to mechanical loading. Such insights could inform targeted therapeutic strategies to enhance bone density and mitigate osteoporosis, particularly given evidence linking reduced Piezo1 expression to osteoblast dysfunction in osteoporosis patients [12, 31].

7 Therapeutic Implications and Future Directions

Exploring the therapeutic implications of mechanotransduction in bone health underscores the importance of mechanosensitive channels, particularly Piezo1. This section emphasizes the therapeutic potential of targeting Piezo1 in bone-related diseases, highlighting its crucial role in bone cell behavior and remodeling processes. Understanding these mechanisms can lead to novel strategies for enhancing bone density and structural integrity.

7.1 Therapeutic Potential of Targeting Piezo1

Targeting Piezo1 offers an innovative approach to treating bone-related diseases like osteoporosis and osteoarthritis. As a key mechanosensitive ion channel, Piezo1 mediates cellular responses to mechanical stimuli essential for bone remodeling and homeostasis [16]. Modulating mechanotransductive pathways via Piezo1 activation could enhance bone density and integrity, providing significant therapeutic benefits.

Activating Piezo1 in osteoblasts to stimulate mechanosensitive signaling pathways is a promising strategy for improving bone formation, especially in conditions like mechanical unloading or osteoporosis. Research indicates that Piezo1 is integral in converting mechanical stimuli into biochemical responses that drive bone formation, with reduced expression linked to impaired osteoblast function in osteoporotic patients. Enhancing Piezo1 activity may counteract bone loss from reduced mechanical loading and improve bone health [18, 35, 12, 13, 31]. This strategy highlights the therapeutic potential of Piezo1 activation in osteoblasts to mitigate mechanical stress deficiencies.

Developing multiresponsive biomaterials integrating various therapeutic modalities is crucial for advancing Piezo1-targeted therapies. Such biomaterials can significantly enhance understanding of biological interactions and optimize manufacturing processes, offering a holistic approach to bone-related diseases, including those complicated by tumors and infections [1, 15, 24]. Dietary interventions like fatty acid supplementation also present non-invasive strategies for managing Piezo1-related pathologies by modulating its activity.

Future research should focus on elucidating the specific roles of identified mechanosensors in vivo and exploring potential therapeutic targets for bone-related diseases [7]. Integrating mechanobiology insights may inform the design of artificial niches to support stem cells for regenerative therapies, offering innovative solutions for bone regeneration and repair.

7.2 Challenges and Future Directions in Bone Mechanobiology

Bone mechanobiology faces challenges that require innovative research strategies to enhance understanding and treatment of bone-related diseases. A significant challenge is integrating biological

factors into existing models, like the FENN model, to improve realism and applicability [39]. Current models often treat healing and remodeling separately, limiting their effectiveness in capturing the complex interplay between these phenomena. Future research should refine models like the MRCDM to incorporate varying mechanical stimuli, better representing interactions between tissue healing and remodeling [41].

The architecture of microtubule networks is crucial in mechanotransduction, and investigating these networks could provide insights into cellular behavior in response to mechanical stimuli [48]. Additionally, optimizing the mechanical properties of piezoelectric materials presents challenges warranting further research [18].

Model refinement is critical for advancing bone mechanobiology. Future efforts should focus on accommodating different anatomical locations and validating models' clinical applicability in vivo [49]. Integrating patient datasets into computational models could enhance accuracy and facilitate the exploration of parametric model repair techniques to optimize diagnosis [47]. Refining mathematical modeling approaches and exploring implications of diseases related to bone remodeling, like osteoporosis, remain essential research directions [40].

Investigating the molecular mechanisms of Piezo1 activation across different cell types and diseases is crucial, as understanding these processes could inform therapeutic strategies [50]. Experimental validation of proposed mechanisms and exploration of physiological processes not explicitly included in current models are necessary for advancing the field [8]. Future improvements could involve extending models to higher spatial dimensions and investigating additional signaling mechanisms related to BMU initiation and termination [38].

7.3 Bio-inspired Materials and Regenerative Medicine

Bio-inspired materials hold significant potential for advancing regenerative medicine, particularly in bone health and repair. These materials mimic the complex hierarchical structure and mechanical properties of natural bone, providing scaffolds that support cell adhesion, proliferation, and differentiation essential for effective tissue regeneration [34]. By emulating bone's mechanosensing capabilities, bio-inspired materials enhance implant integration with host tissue, promoting functional recovery and long-term stability.

Future research should focus on optimizing the mechanical properties of these materials to better replicate the toughness and flexibility of natural bone. This involves examining fundamental principles governing bone mechanosensing mechanisms, which allow bone tissue to dynamically respond to mechanical stimuli and undergo structural adaptations. These mechanisms are critical for maintaining bone homeostasis through balanced interactions between osteoblasts and osteoclasts, ensuring bone mass adjusts in response to varying mechanical loads. Understanding these processes is essential for elucidating the pathophysiology of bone disorders, developing therapeutic strategies for conditions like osteoporosis, and enhancing knowledge of how factors like aging and mechanical unloading impact bone integrity and resilience [34, 30, 16, 8, 31]. Incorporating these principles into regenerative material design can create scaffolds that support bone regeneration and enhance the mechanical resilience of repaired tissue.

Integrating bio-inspired materials with advanced manufacturing techniques, such as 3D printing, can facilitate the creation of patient-specific implants that closely match individual anatomical and biomechanical requirements. This personalized approach to regenerative medicine shows significant potential for improving bone repair and reconstruction outcomes, especially in complex cases involving fractures or extensive bone defects. By leveraging advanced understanding of bone biology, including the roles of various cellular constituents and the development of smart stimuli-responsive biomaterials, this strategy aims to address the unique pathological microenvironments associated with bone injuries. These innovations not only facilitate the restoration of bone to its pre-injury state but also improve treatment efficacy by integrating therapeutic functions tailored to individual patient needs [1, 33, 15].

8 Conclusion

Piezo1 emerges as a critical mechanosensitive ion channel within the realm of mechanotransduction, underscoring its significance in maintaining bone health and offering potential as a therapeutic

target. By converting mechanical stimuli into biochemical signals, Piezo1 regulates the delicate balance between osteoblast and osteoclast activity, which is essential for skeletal integrity. Its role in mechanotransduction pathways is particularly pertinent to osteodegenerative diseases such as osteoarthritis and osteoporosis, where its modulation could provide therapeutic advantages.

The dynamic responsiveness of Piezo1 to mechanical forces enables vital cellular responses necessary for bone adaptation and repair. This survey accentuates Piezo1's involvement in mediating cellular interactions and signaling pathways that influence bone density and cartilage health, highlighting its therapeutic promise for conditions like osteoporosis and osteoarthritis. The integration of Piezo1-targeted strategies with bio-inspired materials and regenerative medicine holds potential for advancing bone health and pioneering novel treatments for bone-related ailments.

Future investigations should focus on unraveling the intricate mechanisms of Piezo1 activation and its interactions with cellular components to harness its full therapeutic potential. By deepening our understanding of Piezo1's role in mechanotransduction and its implications for bone health, this survey lays the groundwork for developing targeted interventions that could markedly improve clinical outcomes in osteodegenerative diseases.

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