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Review

The Role of Piezo Channel Proteins in Aging and Age-Related Diseases: From Molecular Mechanisms to Therapeutic Potential

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ABSTRACT: The accelerating global aging trend has made age-related diseases a critical public health challenge. Piezo1 and Piezo2, as evolutionarily conserved mechanosensitive ion channels, convert mechanical signals such as membrane stretch, matrix stiffness, fluid shear stress, and osmotic pressure into electrochemical signals, mainly Ca^{2+} influx, thereby regulating cell proliferation, apoptosis, inflammation, matrix remodeling, and metabolic homeostasis. During aging, altered tissue mechanics and impaired mechanotransduction are associated with changes in Piezo channel levels, which may contribute to the development and progression of neurodegenerative diseases, musculoskeletal degeneration, cardiovascular and cerebrovascular diseases, organ fibrosis, diabetes, hypertension, and skin aging. Piezo channels may therefore represent potential therapeutic targets for these age-related disorders. However, most evidence supporting these approaches remains preclinical, with small molecules, natural compounds, dietary fatty acids, exercise, ultrasound stimulation, and nanotechnology-based targeted delivery systems showing beneficial effects in experimental models. Despite these advances, challenges including tissue-specific regulation, selective drug development, long-term safety, and clinical translation remain. Further investigation of Piezo channels will provide new insights and intervention targets for promoting healthy aging and treating age-related diseases.

Keywords: Piezo proteins, Aging, age-related diseases, Molecular mechanisms, Mechanical signal, Targeted therapy

1. Introduction

According to the 2022 World Health Organization (WHO) report, the pace of population aging across the globe is accelerating much more rapidly than in previous decades, with both the number and proportion of older individuals steadily increasing [1]. Between 2020 and 2050, the worldwide population of people aged 60 years or older is expected to rise from 1 billion to 2.1 billion, while those aged 80 and above are projected to triple, reaching 426 million [1, 2]. Aging is associated with the decline of tissue and cellular function, and simultaneously significantly increases the risk of various age-related diseases. As the global population ages rapidly and pandemics spread worldwide, diseases such as cardiovascular and cerebrovascular disorders, neurodegenerative conditions, and locomotor and sensory degenerative diseases have emerged as major public health challenges [2-4]. Therefore, anti-aging interventions and related biomarkers represent the most

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promising strategies for health promotion. Targeting age-related factors may offer greater advantages in extending healthspan than addressing each chronic disease individually. However, current therapeutic interventions for aging remain suboptimal and often fail to achieve sustained relief, largely due to an incomplete understanding of the underlying mechanisms. Elucidating these unclear mechanisms is key to laying the foundation for more effective treatments.

Aging is accompanied by progressive alterations in cellular mechanical properties, characterized by increased stiffness, reduced elasticity, and diminished strength across the cardiovascular, musculoskeletal, skin, and immune systems [5, 6]. During this process, diverse cell types, including vascular smooth muscle cells (VSMCs), epithelial cells, cardiomyocytes, cardiac and skin fibroblasts, osteocytes, chondrocytes, intervertebral disc cells, and red blood cells (RBCs), gradually undergo cellular stiffening, which alters their mechanical properties and mechanosensitivity, ultimately impairing cellular responsiveness and tissue function [7]. For instance, aged human fibroblasts exhibit reduced migratory capacity, characterized by shorter migration distances and decreased directionality [8]; aging also compromises force generation in human muscle cells and contractile function in rat VSMCs [9]. The cumulative disruption of cellular mechanics consequently contributes to tissue dysfunction and the development of aging-associated diseases. The extracellular matrix (ECM) is a fundamental mediator of multicellular organization, providing structural connections between cells, facilitating tissue and organ specialization, mediating intercellular communication, and supporting cell survival and differentiation [10, 11]. Its principal components include collagens, elastin, proteoglycans, and cell-binding glycoproteins [12]. With aging, ECM integrity progressively deteriorates due to collagen fragmentation, oxidation, glycation, and protein aggregation, thereby impairing ECM dynamics and promoting tissue fibrosis [13]. In aged rats, for example, increased VSMC stiffness is primarily associated with enhanced collagen deposition and reduced elastin surrounding vascular cells [9]. Meanwhile, mechanical forces within cells and their microenvironment, including tension, contraction, compression, and shear stress, are essential for diverse biological processes. Increasing evidence indicates that aging is accompanied by progressive alterations in these mechanical forces, driven by ECM degeneration [14] and chronic inflammation within the tissue microenvironment [15], together with dysregulation of the intracellular cytoskeleton and mechanosensitive signaling pathways [8]. Moreover, mechanotransduction plays a central role in aging by integrating mechanical cues, including ECM stiffness, cytoskeletal tension, and nuclear deformation. These signals modulate intracellular pathways such as Hippo/YAP, TGF-β/Smad, and mTOR, thereby regulating cell fate, proliferation, and differentiation and ultimately influencing the aging process through subcellular mechanotransduction [16].

Aging is a biological process characterized by a gradual decline in tissue function and regenerative capacity, driven by mechanisms such as cellular senescence, chronic inflammation, and epigenetic changes [17]. The well-established capacity of cells to detect mechanical cues from their surroundings or within themselves is essential for survival and proper function, yet the molecular basis of this mechanosensing has been debated for decades. A transformative advance came in 2010 with the discovery of the Piezo protein family (Piezo1 and Piezo2), which form genuine mechanically activated (mechanosensitive) ion channels, fundamentally reshaping our view of mechanosensing at the molecular level [18, 19]. In mammals, Piezo channels display distinct tissue and cellular distributions: Piezo2 is largely restricted to sensory neurons and contributes to mechanotransduction, whereas Piezo1 is broadly expressed throughout the body and participates in a variety of physiological functions [19]. Although both are mechanosensitive ion channels, the depth and nature of the evidence supporting their roles in aging and age-related diseases differ substantially. Compared with Piezo1, evidence linking Piezo2 to age-related pathophysiology remains limited and is largely confined to specific sensory and neurological contexts. Nevertheless, accumulating studies suggest that Piezo channels, particularly Piezo1, may contribute to the pathophysiology and progression of various age-related diseases through their responses to mechanical cues. These include cardiovascular and cerebrovascular disorders, degenerative musculoskeletal conditions, and neurodegenerative diseases. This narrative review discusses the structural characteristics, gating mechanisms, and pharmacological properties of Piezo channels, with a focus on recent advances in their roles and underlying signaling mechanisms in age-related diseases. It also critically examines differences in the scope and strength of the available evidence for Piezo1 and Piezo2, highlighting current knowledge gaps and directions for future research.

2. Structure, function, and mechanotransduction mechanisms of Piezo proteins

Mechanotransduction is a fundamental ability of living organisms to receive and respond to physical signals from internal and external environments. In mammals, mechanotransduction is involved in many physiological processes, such as gravity, touch, sound, proprioception,

airflow, blood pressure, and vascular development [20]. Accurate and efficient mechanotransduction is critical for maintaining normal organ function, whereas its dysfunction or disruption can contribute to a broad spectrum of diseases, including cardiovascular disorders, neurological conditions, cancer metastasis, and osteoporosis [21-23]. Widely present in cell membranes, mechanosensitive ion channels are a class of force-sensitive proteins that respond to diverse mechanical stimuli and convert extracellular mechanical signals into intracellular electrochemical signals [24]. In 2010, using patch-clamp electrophysiology and a genome-wide RNA interference screen, Ardem and colleagues discovered a new family of mammalian mechanosensitive channels (MSCs)—the Piezo proteins—in mouse neuroblastoma cells [18]. This family consists of two large multi-transmembrane proteins, Piezo1 (Fam38A) and Piezo2 (Fam38B), which are widely distributed in the cell membrane lipid bilayer and share highly similar gene sequences and structural features, yet lack homology with other previously known force-sensitive proteins [25]. Currently, Piezo1 and Piezo2 are the most extensively studied members of this family; they play a key role in a variety of physiological and pathological processes, which is the focus of our discussion.

Over the past ten years, numerous investigations have focused on illustrating the molecular architecture of Piezo proteins. High-resolution structural characterization of Piezo1 and Piezo2 by cryo-electron microscopy (cryo-EM) has markedly advanced our comprehension of the structure–function coupling underlying these intricate mechanosensitive Piezo channels [26, 27]. In 2015, Ge and colleagues first reported the molecular architecture of mouse Piezo1 [28]. Through an integrated approach employing protein engineering, negative-stain and cryo-EM, and X-ray crystallography, they determined that Piezo1 is a large, homotrimeric channel protein featuring a distinctive three-bladed propeller-like structure. This architecture comprises a central pore module for ion conduction, capped by an extracellular domain, and encompasses 2547 amino acids. Subsequent high-resolution structural studies, complemented by mutagenesis experiments targeting key residues, have elucidated critical aspects of the channel's gating mechanism [26, 29]. Mouse Piezo2 consists of 2822 amino acids and shares approximately 42% sequence identity with Piezo1. Both channels exhibit a striking 38-transmembrane topological arrangement, which includes an N-terminal region, a C-terminal pore module, and connecting beam and anchor domains [28, 30].

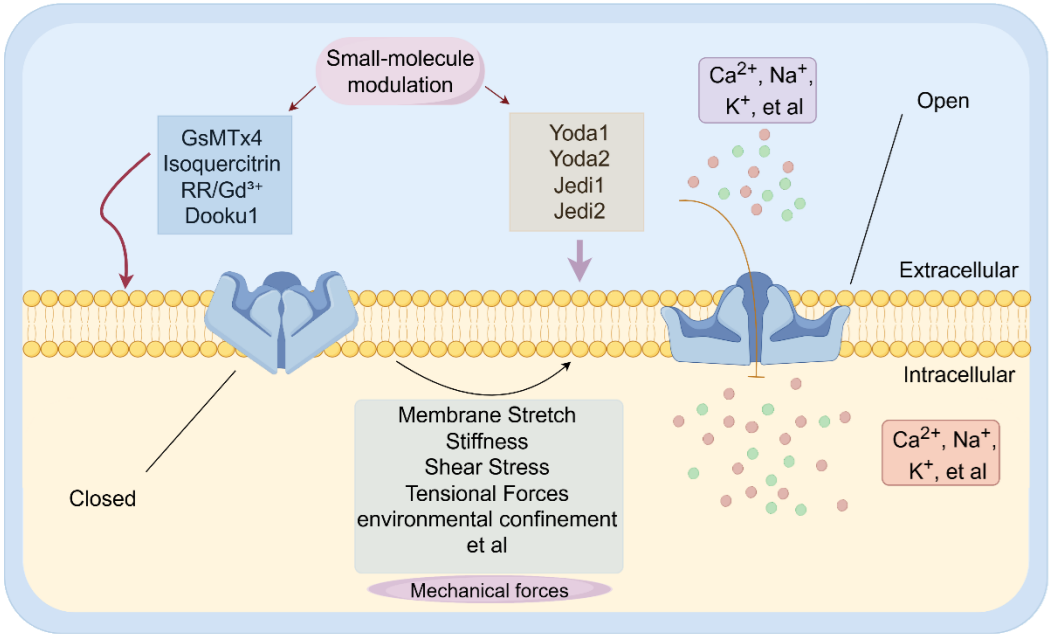


Figure 1. Structure and regulation of Piezo1 channel. The mechanosensitive ion channel Piezo1, located on the plasma membrane, can be regulated by various mechanical stimuli such as membrane stretch, stiffness, shear stress, tensional forces, and environmental confinement. Upon activation, the channel allows sodium and calcium ions to enter the cytoplasm, thereby mediating a range of cellular responses. Piezo1 levels are modulated by mechanical and chemical cues, whereas small-molecule modulation of Piezo channels regulate its channel activity. Abbreviations: Ca^{2+}, calcium ion; Na^{+}, sodium ion; K^{+}, potassium ion; RR, ruthenium red; Gd^{3+}, gadolinium ion.

Piezo channels exhibit fast activation and voltage-dependent inactivation, and their kinetic properties remain largely similar across a wide range of cell types [31]. Piezo channel activation and regulation are governed by both pure mechanical stimuli and protein-protein interactions. Notably, mammalian Piezo1 can be directly gated by membrane stretch—a property preserved throughout evolution [28, 30]. Moreover, Piezo proteins are capable of forming functional channels on their own, without requiring additional pore-binding auxiliary proteins or cytoskeletal components for activation [32]. In HEK293 cells cultured under conditions largely devoid of cytoskeletal elements, Piezo1 can be activated by membrane blebbing triggered by lipid bilayer tension [33]. Additionally, in a droplet-based lipid bilayer setup, an osmotic gradient alone—without any additional intracellular components—suffices to activate Piezo1 [34]. Piezo2 encodes the pore-forming subunit of the mechanosensitive Piezo channel, which mediates mechanically activated currents involved in touch and pain perception [35]. Furthermore, Piezo channels have been shown to respond to a broad spectrum of mechanical stimuli, including membrane stretch, fluid shear flow, cell indentation, substrate stiffness, osmotic stress, matrix roughness, and environmental confinement [18, 36] (Fig. 1).

3. Piezo channels in the biology of aging

Although Piezo channels were initially recognized as rapid mechanosensors that convert mechanical forces into Ca^{2+} signals, growing evidence suggests that they also contribute to long-term cellular adaptation. Aging involves mitochondrial dysfunction, chronic inflammation, ECM remodeling, and altered tissue mechanics, which can continuously engage mechanosensitive pathways [37]. Through coupling mechanical cues to Ca^{2+}-dependent signaling, Piezo1 and Piezo2 may link age-related changes in the mechanical microenvironment to cellular dysfunction. Dysregulated Piezo signaling may therefore contribute to key aging features, including inflammation, mitochondrial dysfunction, and cellular senescence.

3.1 Piezo channels and mechanobiology across timescales in cellular aging

Aging may alter how cells integrate transient mechanical inputs over time, thereby converting repeated short-lived signals into persistent cellular states [38]. Among the fastest mechanosensory systems, Piezo channels provide a direct interface between mechanical stimulation and intracellular signaling. Piezo1 and Piezo2 can convert mechanical stimuli into electrical signals within milliseconds and induce Ca^{2+} oscillations, indicating that mechanical information can be encoded not only by signal magnitude but also by its temporal pattern [38, 39]. Importantly, mechanical signaling operates across multiple temporal regimes. Rapid mechanical stress waves can transmit tensile perturbations across cells and reach nuclear compartments within milliseconds, whereas slower biochemical processes, including FAK-mediated transcriptional reprogramming and chromatin remodeling, occur over minutes to hours, facilitating long-term adaptation to chronic mechanical stimuli. This temporal organization allows cells to simultaneously respond to immediate mechanical challenges and integrate persistent environmental cues, such as matrix stiffening, through a unified mechanobiological framework [38, 40].

In this context, recurrent Piezo-dependent Ca^{2+} pulses may represent repeated mechanical inputs that are progressively integrated rather than independently resolved. This concept is consistent with the broader timescale framework of mechanobiology, in which membrane events occur rapidly, whereas cytoplasmic remodeling and nuclear responses develop over progressively longer timescales [38]. Mechanical information can therefore persist beyond the initiating stimulus through molecular turnover, transcriptional regulation, epigenetic remodeling and cellular mechanical memory [41-43]. Indeed, transient mechanical force has been shown to induce chromatin decondensation and increased nucleoplasmic protein mobility that persist for tens of minutes after force cessation, demonstrating that a short mechanical episode can leave a measurable nuclear memory [43]. With prolonged mechanical exposure, chromatin organization and histone acetylation can undergo persistent and partly irreversible remodeling, providing a potential molecular substrate for longer-term mechanical memory [42]. Direct force transmission to chromatin can also rapidly increase transcription, further illustrating the coupling between mechanical inputs and gene regulation [40]. These observations suggest a temporal continuum in which repeated rapid Piezo-mediated Ca^{2+} events may be incorporated into progressively slower nuclear regulatory processes. This framework is particularly relevant to aging because impaired proteostatic turnover is associated with the accumulation of damaged proteins and age-related cellular dysfunction [44]. Thus, an age-dependent reduction in the capacity to resolve or replace mechanically perturbed cellular components could extend the biological consequences of otherwise transient mechanosensory events. Importantly, it supports a multiscale model in which recurrent Piezo-dependent mechanical signals provide rapid inputs that can be temporally integrated into longer-lasting transcriptional,

chromatin and proteostatic states, thereby offering a mechanobiological framework for understanding how transient mechanical events may contribute to persistent phenotypes during aging [38].

Cellular senescence is accompanied by profound alterations in the spatiotemporal dynamics of Ca^{2+} signaling rather than simply an increase in intracellular Ca^{2+} levels [45]. Senescent cardiomyocytes exhibit increased Ca^{2+} peak amplitude and area under the curve, together with prolonged Ca^{2+} clearance and altered oscillatory frequency, highlighting a substantial remodeling of Ca^{2+} signal dynamics during senescence [46]. Moreover, Ca^{2+} signaling can differentially regulate cell fate according to its temporal characteristics, with experimental modeling showing that Ca^{2+} oscillation amplitude can exert a stronger influence on downstream cell-death signaling than oscillation frequency [45], while Ca^{2+} fluxes and Ca^{2+} transfer between the endoplasmic reticulum and mitochondria are recognized as important regulators of cellular senescence [47]. Recent work further emphasizes that Piezo1-derived Ca^{2+} signals are decoded by mitochondria according to their spatial and temporal dynamics, thereby influencing the balance between cellular adaptation and pathological outcomes such as mitochondrial stress, inflammation, and senescence [48]. Collectively, these findings suggest that the biological consequences of Piezo1/2 activation may depend not only on the magnitude of individual Ca^{2+} transients but also on their duration, frequency, recovery kinetics, and cumulative Ca^{2+} burden. However, whether Piezo1/2-mediated cellular senescence is determined predominantly by peak Ca^{2+} amplitude or by the time-integrated Ca^{2+} load remains poorly understood.

3.2 Chronic inflammation

Under non-physiological mechanical stress, tissue injury and inflammation are often accompanied by changes in the mechanical microenvironment. As a mechanosensitive channel, Piezo1 therefore participates in the initiation, progression, and prognosis of inflammation [49]. For example, in aortic stenosis, monocytes sense shear stress through Piezo1, promoting their activation and adhesion to endothelial cells and thereby contributing to valvular inflammation [50]. During chronic inflammation, Piezo1 detects alterations in microenvironmental homeostasis and modulates cellular functions, while its dysfunction may accelerate inflammatory progression. Piezo1-mediated Ca^{2+} signaling regulates inflammation through multiple pathways, including MAPK/ERK, NF-κB, NLRP3, AKT/mTOR, and CaMKII-Mst1/2-Rac, which collectively participate in regulating diverse cellular processes such as proliferation, differentiation, migration, and apoptosis [23, 51-53]. In endothelial cells, for instance, Piezo1 activation induces inflammatory responses via the NF-κB pathway. Mechanical stress activates Piezo1, leading to increased intracellular Ca^{2+} levels, NF-κB activation, and subsequent release of inflammatory cytokines, including TNF-α, IL-1β, and IL-6, thereby contributing to atherosclerotic inflammation [54]. Although the specific targets and pathways vary across diseases, Piezo1-mediated regulation of intracellular Ca^{2+} and downstream signaling represents a common mechanism linking mechanical stimuli to inflammatory responses. Recent studies indicate that Piezo channels are key regulators of mechano-inflammation. Piezo2, mainly expressed in sensory neurons, promotes mechanically induced inflammatory signaling and mediates neuroimmune crosstalk, inflammatory pain, and tissue inflammation [55]. In orofacial inflammation models, Piezo2 blockade reduces IL-1β-induced inflammatory and neuropathic pain behaviors, indicating its essential role in transmitting inflammatory mechanical signals [56]. Moreover, altered Piezo expression in inflamed human pulp tissues suggests that inflammatory environments modulate Piezo2-dependent mechanosensation and contribute to pathological mechanical hypersensitivity [57]. Collectively, Piezo channels function as critical mechanotransducers linking mechanical stimuli to inflammatory responses.

3.3 Mitochondrial dysfunction

Increasing evidence supports a functional link between Piezo1 signaling and mitochondrial regulation, through which mechanical stimuli modulate mitochondrial activity, energy homeostasis, and cell fate [58]. Under physiological conditions, this coupling matches mitochondrial output to mechanical demand. However, excessive or sensitized Piezo1 activation may cause mitochondrial Ca^{2+} overload, oxidative stress, membrane potential loss, impaired quality control, and progressive mitochondrial damage. Inflammation, metabolic disturbances, oxidative burden, and matrix stiffening further reduce mitochondrial capacity to buffer Ca^{2+} and reactive oxygen species (ROS), narrowing the safe coupling range and increasing the likelihood of Piezo1-mediated injury [48]. Persistent Piezo1–mitochondrial Ca^{2+} dysregulation may consequently promote cellular senescence. Sustained Ca^{2+} influx can maintain mitochondrial stress beyond the adaptive range; in chondrocytes, nucleus pulposus (NP) cells, and Leydig cells, Piezo1 activation is associated with mtROS accumulation, impaired autophagy or mitochondrial quality control, and activation of senescence-associated programs [59-61]. Conversely, insufficient physiological input may also induce senescence when Piezo1-dependent

support is lost. In temporomandibular cartilage and the periodontal complex, unloading impairs mitochondrial fusion, antioxidant defense, and remodeling capacity, favoring p16-linked senescence [62, 63]. Thus, both excessive and insufficient Piezo1 activation can disrupt the safe coupling range, while persistent but sublethal mitochondrial stress may favor senescence, contributing to tissue degeneration and remodeling failure [62, 63]. In fibroblast senescence, Transglutaminase 2 (TGM2), a multifunctional calcium-dependent enzyme involved in post-translational protein modification and stress responses, promotes cellular senescence partly by repressing the mechanosensitive ion channel Piezo2, which is associated with calcium-dependent mitochondrial dysfunction and subsequent activation of cGAS-STING signaling. Conversely, Piezo2 knockdown counteracts the anti-senescent effects of TGM2 suppression [64]. These studies indicate that Piezo channels are key regulatory factors linking calcium signaling, mitochondrial homeostasis, and cellular senescence.

3.4 Age-related tissue stiffening

Aging involves not only intracellular molecular and metabolic changes but also remodeling of the tissue mechanical microenvironment, characterized by ECM remodeling and increased tissue stiffness [65]. In the aging testis, enhanced ECM deposition and matrix stiffening activate Piezo1-mediated Ca^{2+} signaling, leading to mitochondrial dysfunction, excessive ROS production, impaired stem Leydig cell homeostasis, and age-related testosterone decline [59]. Similarly, a stiffened hippocampal matrix mimicking aging promotes Piezo1 activation, contributing to neural stem cell dysfunction and senescence [66]. In vascular tissues, aging impairs vascular smooth muscle cell mechanosensitivity through altered Piezo1-dependent mechanotransduction, while increased ECM rigidity activates Piezo1-mediated Ca^{2+} influx and affects smooth muscle cell volume regulation [67, 68]. In skeletal muscle, age-related ECM remodeling and stiffness promote Piezo1-dependent stromal cell activation and inflammation, linking mechanical alterations to inflammaging [65]. Importantly, the relationship between Piezo1 and the ECM appears to be bidirectional, as stiffness-dependent Piezo1 signaling can also regulate ECM remodeling by mesenchymal stem cells, suggesting a potential ECM stiffness–Piezo1–ECM remodeling positive-feedback loop [69]. Although direct evidence connecting aging-associated tissue stiffening with Piezo2 dysfunction remains limited, recent studies suggest that Piezo2 can sense ECM mechanical alterations. In pulmonary fibrosis, matrix stiffness induces Piezo2 expression in fibroblasts, whereas Piezo2 inhibition reduces stiffness-driven myofibroblast differentiation and fibronectin expression, highlighting its role in mechanotransduction during pathological remodeling [70]. Collectively, age-related ECM stiffening represents a conserved mechanical feature across tissues, with Piezo channels, particularly Piezo1, converting altered ECM mechanics into Ca^{2+}-dependent signals that contribute to mitochondrial dysfunction, cellular senescence, chronic inflammation, and tissue functional decline.

Collectively, these findings highlight Piezo channels, particularly Piezo1, as key mechanotransducers linking age-associated alterations in tissue mechanics to Ca^{2+}-dependent signaling and cellular dysfunction across tissues, as summarized in Figure 2.

4 Age-related diseases: disease-specific roles of Piezo channels

Age-related alterations in ECM composition, tissue stiffness, cytoskeletal organization, and mechanical loading can reshape the tissue mechanical microenvironment and may modulate Piezo1/2-mediated mechanosensing and Ca^{2+} signaling [24, 59]. These changes can subsequently influence inflammatory responses, mitochondrial function, cellular metabolism, cellular senescence, and tissue remodeling, thereby potentially contributing to the development and progression of age-related diseases. Conversely, disease progression, tissue injury, and chronic inflammation can further induce ECM remodeling, fibrosis, and tissue stiffening, thereby altering the local mechanical environment and enhancing Piezo channel-mediated mechanosignaling. This bidirectional interaction may establish a feedback loop that amplifies tissue dysfunction. Therefore, Piezo1/2 should not be regarded simply as initiating drivers of aging. Rather, their roles are likely to depend on the specific cellular, mechanical, and pathological context, in which they may function both as mechanosensitive responders to age-related mechanical changes and, under certain pathological conditions, as amplifiers of age-associated tissue dysfunction.

4.1 Neurodegenerative diseases

Neurodegenerative diseases cause progressive neuronal or myelin damage, leading to neurological dysfunction that worsens with age [71]. Affected older adults suffer memory loss, cognitive impairment, sensory and motor deficits, and homeostatic imbalance, severely reducing quality of life and imposing substantial caregiving and economic costs [72]. Current clinical therapies offer only limited early-stage symptomatic relief, not a cure. Recently, Piezo proteins have attracted attention as

potential regulators in neurodegenerative diseases, although their roles and therapeutic potential require further investigation.

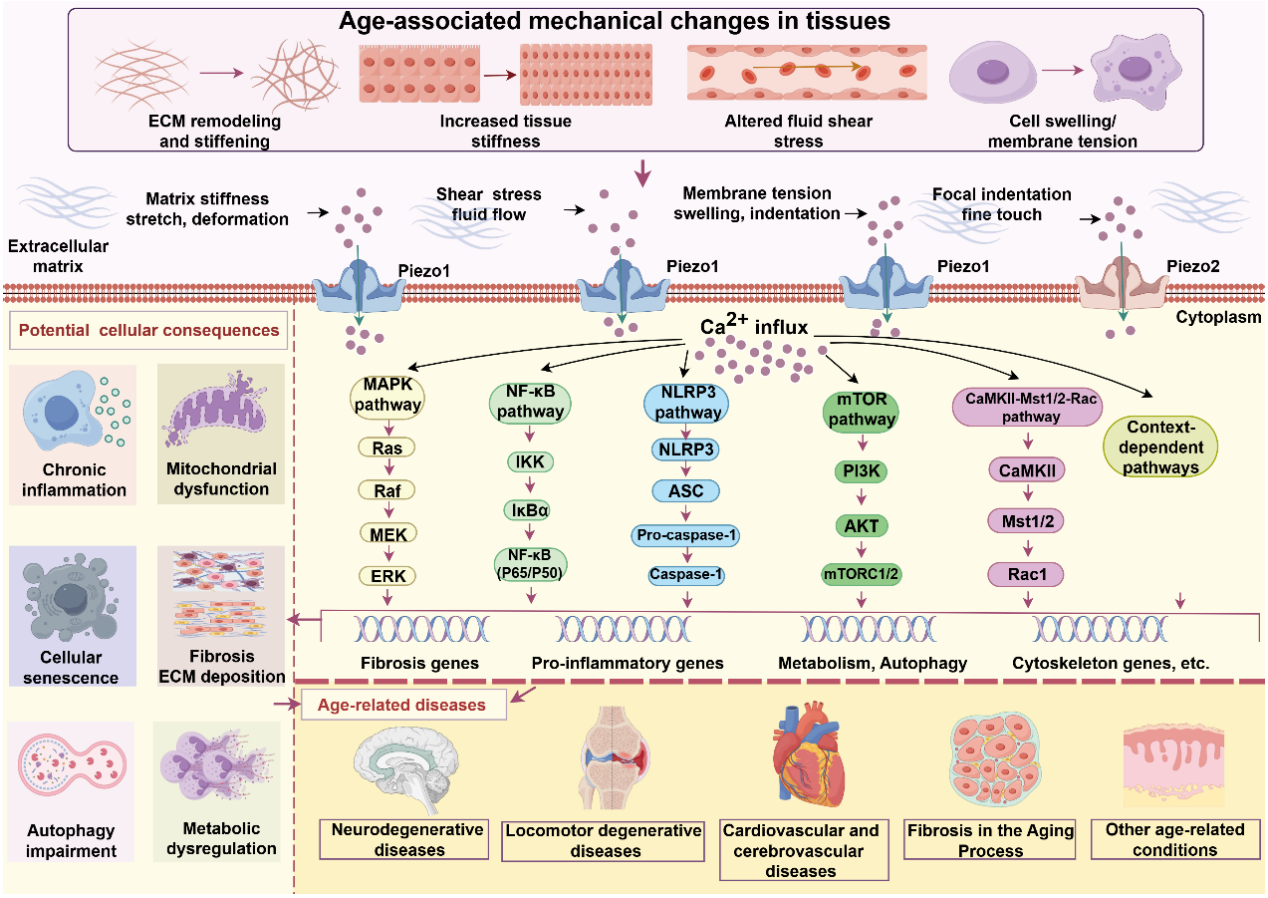


Figure 2. Piezo-mediated mechanotransduction links age-associated mechanical changes to tissue degeneration and age-related diseases. Aging alters tissue mechanics through ECM remodeling, increased stiffness, disturbed fluid shear stress, and changes in cellular tension. These mechanical stimuli activate Piezo1/2 channels, inducing Ca^{2+} influx and engaging downstream signaling pathways, including MAPK, NF-κB, NLRP3 inflammasome, mTOR, and CaMKII-Mst1/2-Rac pathways. Subsequent transcriptional and cellular responses regulate inflammation, metabolism, autophagy, cytoskeletal remodeling, fibrosis, and cellular senescence. Dysregulated Piezo signaling may therefore contribute to the initiation or progression of multiple age-related diseases, including neurodegeneration, musculoskeletal degeneration, cardiovascular disorders, and fibrosis. Abbreviations: ECM, extracellular matrix; Ca^{2+}, calcium ion; MAPK, mitogen-activated protein kinase; Ras, rat sarcoma; Raf, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor kappa B; IKK, IκB kinase; IκBα, inhibitor of nuclear factor kappa B alpha; NLRP3, NLR family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; mTORC1/2, mechanistic target of rapamycin complex 1/2; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; Mst1/2, mammalian STE20-like kinase 1/2; Rac1, Ras-related C3 botulinum toxin substrate 1.

4.1.1 Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by cognitive decline and the accumulation of misfolded protein aggregates, particularly amyloid-beta (Aβ) plaques [73]. Following the onset of AD, irreversible pathological progression may continue for approximately 20 years before clinical manifestations become evident. ECM proteins are among the few biological components capable of persisting over such a prolonged period [74]. Thus, chronic ECM degeneration and/or remodeling may represent an important component of both aging and AD pathogenesis. Aging remodels the ECM—increasing stiffness via cross-linking and glycation and altering collagen /elastin—which alters mechanosensitive signaling in the brain [75]. In the progression of AD, activated microglia produce pro-inflammatory cytokines and engage in

phagocytosis, serving as key regulators of the pathological environment [76]. Human studies show increased microglia surrounding Aβ plaques specifically upregulate the expression of the Piezo1 protein, while in vitro experiments indicate that Piezo1 senses Aβ fibril stiffness to promote Ca^{2+}-dependent microglial clustering and phagocytosis. Consistently, Piezo1 deficiency aggravates Aβ pathology and cognitive decline, whereas its pharmacological activation reduces Aβ burden and cognitive impairment in 5×FAD mice [21]. Ca2+ binds calmodulin to activate CaMKII and protein kinase C (PKC) and modulate calcineurin/GSK-3β signaling, linking ionic imbalance to tau pathology [77, 78]. Blood bacterial extracellular vesicles containing lipopolysaccharide (LPS) can cross the blood–brain barrier (BBB), activate microglial Piezo1, and drive excessive synaptic pruning via the C1q–C3 complement pathway [79]. In vitro experimental results show that, under LPS stimulation, activation of Piezo1 further upregulates the mRNA and protein expression levels of the pro-inflammatory factors IL-1β, IL-6, and TNF-α in microglia, whereas inhibition or knockout of Piezo1 significantly reduces the LPS-induced release of these pro-inflammatory factors [80]. Thus, Piezo1-dependent mechanosensing enhances microglial clearance of stiff Aβ deposits but may also promote inflammation and maladaptive synaptic loss in AD.

Piezo1 is highly responsive to changes in local membrane tension, shear stress, and ECM stiffness; its expression levels in astrocytes are also altered in brain regions affected by AD [81]. In the healthy human brain, Piezo1 mRNA is detected in neurons but not astrocytes. In contrast, post-mortem AD brain analysis showed reduced neuronal Piezo1 mRNA expression and increased expression in astrocytes surrounding amyloid plaques [82]. In a separate study, an aging transgenic rat model of AD (TgF344-AD) was used to examine the expression of Piezo1, a mechanosensitive ion channel, in astrocytes responding to amyloid plaques. Expression levels of Piezo1 were found to increase with age in the hippocampus and cortex of 18-month-old wild-type rats. This age-related increase was more pronounced in the hippocampus of TgF344-AD rats than in age-matched wild-type controls. Moreover, recurrent urinary tract infections induced by E. coli—a frequent complication in patients with AD—further elevated Piezo1 expression in both the hippocampus and cortex of TgF344-AD animals [83]. Together, animal studies have shown that both aging and peripheral infection can promote the upregulation of mechanosensitive ion channels, such as Piezo1, in astrocytes associated with amyloid plaques.

RBCs rely on the highly mechanosensitive and calcium-permeable Piezo1 channel to navigate the narrowest capillaries throughout the circulatory system. This channel works in close coordination with the Gárdos K+ channels to regulate the volume homeostasis of RBCs [84]. Sitnikova et al [85]. showed Aβ peptides alter RBC biomechanics (reduced membrane stiffness) and modify Piezo1-mediated Ca2+ responses: Yoda1-evoked Ca2+ influx and Piezo1-dependent shape changes were markedly greater in RBCs from mild cognitive impairment (MCI) and early-AD patients than in healthy controls (HCs). Machine-learning models that included Yoda1-stimulated Piezo1 signals improved classification of MCI/AD versus controls beyond many conventional blood biomarkers, indicating elevated RBC Piezo1 activity as a promising peripheral biomarker for early AD-related cognitive decline.

Piezo2 is a homolog of Piezo1, which has previously been implicated in the clearance of amyloid-β, suggesting that mechanosensitive Piezo channels may contribute to AD pathology [18]. In a genome-wide association study involving Hispanic participants from the AD Sequencing Project, a common variant in Piezo2 on chromosome 18 was identified as protective against AD, with a p-value just beyond genome-wide significance [86]. Emerging evidence linking repeated low-level blast overpressure exposure in military personnel to neurocognitive decline, neuroinflammation, and neurodegeneration suggests that such repetitive exposure may induce subclinical symptoms resembling mild traumatic brain injury, with progressive vascular and cellular changes that could contribute to neurodegeneration [87]. Following shock wave exposure, Piezo2 levels in rat brains become dysregulated, with concentrations increasing after repeated moderate-intensity blasts—suggesting that such explosions may alter the brain's mechanical sensitivity, contribute to cellular damage, and potentially link blast injury to neurodegenerative disease [88] (Table 1).

4.1.2 Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating neurodegenerative disease of the CNS, characterized by focal white- and gray-matter plaques from immune infiltration across a disrupted BBB, leading to inflammation, demyelination, reactive gliosis and axonal loss [89]. Cerebral shear elasticity was markedly lower in patients with primary or secondary chronic-progressive MS than in those with early relapsing-remitting MS [90]. Patients with clinically isolated syndrome, representing the first clinical manifestation of potential MS, likewise showed reduced brain viscoelasticity [91]. Unlike AD, Piezo1 is downregulated in the MS brain, with significantly lower Piezo1 mRNA levels in MS white matter (WM) than in non-MS (control) WM. However, within the same MS brains, Piezo1 mRNA expression did not differ between MS plaques and

healthy-appearing WM. These findings suggest that Piezo1 downregulation in MS is not restricted to demyelinated or degenerated regions but occurs across the brain [92]. In experimental autoimmune encephalomyelitis (EAE), Piezo1 is suppressed and its inhibition promotes remyelination [93]. T-cell–specific Piezo1 deletion reduces EAE severity by enhancing TGF-β signaling and expanding regulatory T (Treg) cells, while leaving conventional T-cell activation, proliferation and effector differentiation intact; Treg-specific deletion alone also ameliorates disease [94].

Table 1. Multi-mechanistic regulatory network of Piezo proteins in age-related diseases.

Disease	Piezo subtype	Expression change	Major cell types	Functional direction of modulation (in general)	Key mechanisms	Evidence level	Refs
Neurodegenerative diseases							
Alzheimer's disease	Piezo1	↑ in plaque-associated microglia/astrocytes, ↓ neurons	Microglia, astrocytes, neurons	Protective effect of activation	Ca^{2+}-dependent microglial clustering, C1q–C3 signaling, inflammatory response	Human tissue/clinical samples; in vitro; animal models	[21, 77-85]
	Piezo2	Genetic variant potentially protective	—	Unclear	mechanosensitivity/neurodegeneration	GWAS; animal models	[86-88]
Multiple sclerosis	Piezo1	↓ in MS brain	OPCs, oligodendrocytes, T cells	Protective effect of inhibition	TGF-β/Treg signaling, OPC migration and differentiation	Human brain tissue; EAE models; in vitro; cell-specific KO	[92-96]
	Piezo2	No direct evidence	—	Unclear	—	—	—
Multiple system atrophy	Piezo1	↓ urinary exfoliated cells	urinary exfoliated cells	Unclear	Potential diagnostic biomarker	Human multi-cohort study	[99]
	Piezo2	No direct evidence	—	Unclear	—	—	—
Locomotor degenerative diseases							
Osteoarthritis	Piezo1	↑ under overload/inflammation	Chondrocytes, synovial cells	Pathogenic effect of activation	Ca^{2+}-NFκB/NLRP3, cGAS-STING, YAP signaling	Human tissue; OA animal models; in vitro; cKO/pharmacological studies	[51, 52, 106-113]
	Piezo2	Expressed in nociceptors	Sensory neurons	Inhibition reduces pain	NGF-mediated mechanosensation and pain signaling	animal models	[114]
Osteoporosis	Piezo1	↓ with aging	Osteocytes, osteoblasts, BMSCs	Protective effect of activation	Wnt signaling, YAP-CCN, AMPK/SIRT1/PGC1α	Human tissue evidence; animal KO; in vitro; pharmacological studies	[22, 119-126]
	Piezo2	Skeletal developmental role	Skeletal cells	Physiological maintenance role	skeletal development/homeostasis	Human genetic studies; animal models	[114]
IVDD	Piezo1	↑ in degenerated NP/CEP	NP cells, CEP cells, AF cells	Pathogenic effect of activation	Ca^{2+}/YAP, NFκB/NLRP3, mitochondrial dysfunction, ferroptosis	Human surgical tissue; in vitro; aged/instability models; cKO	[107, 132-141]
	Piezo2	No direct evidence	—	Unclear	—	—	—
Cardiovascular and cerebrovascular diseases							
Atherosclerosis	Piezo1	↑ in plaque endothelium; activated by disturbed flow/oxLDL	Endothelial cells, macrophages	Pathogenic effect of activation	Ca^{2+}/CaMKII–FAK/YAP, KDM5B, NF-κB, anti-ferroptotic signaling	ApoE−/− models; endothelial/myeloid KO; in vitro	[54, 146-154]
	Piezo2	No direct evidence	—	Unclear	—	—	—
Calcific aortic valve disease	Piezo1	↑ with matrix stiffness/OSS	VICs	Protective effect of inhibition	Ca^{2+}–YAP/GLS1–RUNX2 → osteogenic differentiation and	Animal models; VICs in vitro; pharmacological	[160, 161]

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					calcification	studies	
	Piezo2	No direct evidence	—	Unclear	—	—	—
Heart failure	Piezo1	↑ in failing heart	Cardiomyocytes, fibroblasts	Protective effect of inhibition	CaMKII–HDAC4–MEF2, fibrosis, Ca^{2+} signaling	Human tissue; mouse/rat models; in vitro; KO/agonist studies	[164-167]
	Piezo2	↑ in failing heart	cardiac tissue, Fibroblasts	Protective effect of inhibition	TET3–Piezo2 → fibroblast activation/fibrosis	Human tissue; mouse models; in vitro	[168]
Myocardial infarction	Piezo1	↑ in failing/MI hearts	Cardiomyocytes, sensory neurons, macrophages	Pathogenic effect of activation	CaMKII/RyR2, IL-6, ferroptosis/efferocytosis → injury, inflammation, adverse remodeling	Human failing-heart tissue; mouse MI models; in vitro	[164, 171-173]
	Piezo2	no significant change	—	Unclear	—	—	[171]
Stroke	Piezo1	↑ after ischemia/hemorrhage	Endothelial cells, astrocytes, neurons	Protective effect of inhibition	Ca^{2+} influx, AMPK-mTOR, Wnt7b signaling	Human tissue; rodent models; in vitro; KO/inhibitor studies	[176-179, 181, 182]
	Piezo2	↑ after ICH mass effect	neurons	Protective effect of inhibition	ERK-related iron metabolism	Animal models	[183]
Fibrosis in the Aging Process							
Fibrosis	Piezo1	↑ with tissue stiffness/fibrosis	Fibroblasts, VSMCs	Pathogenic effect of activation	ECM stiffness–Piezo1–Ca^{2+} feedback loop, TGF-β	Aged/animal models; cell-specific KO; in vitro	[18, 186-189]
	Piezo2	↑ in fibrotic fibroblasts	Fibroblasts	Pathogenic effect of activation	m^6A/YTHDF1, TGF-β → myofibroblast activation	Human tissue; Animal models; in vitro	[64, 70, 186, 190]
Other age-related conditions							
Diabetes	Piezo1	↑ in human islet samples	β-cells, neurons, microglia, endothelial cells	Pathogenic effect of activation	calcium-dependent exocytosis, NO, mitochondrial dysfunction, neurotoxicity	Human samples; diabetic animal models; in vitro	[194-198]
	Piezo2	↑ in DKD; altered in neuropathy	Mesangial cells,	Unclear	ECM/5-HT signaling → renal fibrosis, gastric/sensory effects	Human samples; diabetic animal models; in vitro	[199-201]
Hypertension	Piezo1	↑ models of hypertension	VSMCs	Pathogenic effect of activation	AKT, ERK, and CaMKII via Ca^{2+}-dependent signaling	Rodent models; in vitro	[203-208]
	Piezo2	altered in baroreceptors/renal tissues; ↓ in hypertensive NG	Sensory neurons	Unclear	Nedd4-2/baroreflex signaling → BP regulation	Rodent models; optogenetics; in vitro	[209-212]
Skin aging	Piezo1	activated by dermal stiffness; induced by PLLA/PDLLA/RF	Epidermal stem cells	Protective effect of activation	Ca^{2+}-ERK/AKT/mTOR signaling	Animal models; in vitro	[216-220]
	Piezo2	↓ in aged mechanosensory cells	Merkel/Meissner cells	Activation suppresses mechanical itch	BDNF–TrkB → tactile sensation/itch	Animal models; in vitro	[222, 223]

Oligodendrocyte precursor cells (OPCs) and oligodendrocytes are mechanosensitive, and ECM stiffening—which increases with age and occurs in chronic demyelinating lesions—impairs their proliferation, migration and differentiation [95, 96]. Piezo1 is expressed in oligodendrocytes/OPCs in human brain; blocking Piezo1 with GsMTx4 boosts MO3.13 cell proliferation and migration, whereas Yoda1 activation suppresses them [92]. A cautious interpretation is that Piezo1 downregulation in MS brains may represent a feedback response to progressive microenvironmental stiffening. Reduced Piezo1 expression may help restore cellular mechanosensing and thereby promote OPC proliferation and migration. Therefore, extensive research

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using MS animal models and further in vitro functional assays are needed to understand the consequences or potential benefits of Piezo1 and Piezo2 in the diseased brain (Table 1).

4.1.3 Multiple system atrophy

Multiple system atrophy (MSA) is a fast-progressing neurodegenerative disease marked by the accumulation of α-synuclein within glial cytoplasmic inclusions in oligodendrocytes, which results in extensive oligodendrocyte dysfunction, demyelination, and neuronal loss [97]. Clinically, MSA manifests as autonomic dysfunction, parkinsonism, and cerebellar ataxia, but currently no disease-modifying treatments are available. Although α-synuclein-based tests can assist in differential diagnosis, reliable biomarkers remain scarce [98]. Using multiple analytical techniques across three independent cohorts, researchers quantified Piezo1 expression in urinary exfoliated cells from 76 patients with MSA, 103 with idiopathic Parkinson's disease (iPD), 59 with progressive supranuclear palsy (PSP), and 126 HCs. In the discovery cohort, Piezo1 levels were significantly lower in MSA patients than in HCs, iPD, and PSP (area under the curve: 0.9421, 0.8218, and 0.8036, respectively)—findings validated in two additional cohorts, supporting consistently reduced Piezo1 expression as a distinguishing feature of MSA [99] (Table 1).

Overall, Piezo channels may contribute to neurodegenerative disease through disease-specific regulation of mechanosensing, neuroinflammation, protein clearance, and myelin homeostasis. However, their effects are highly context- and cell-type-dependent, with Piezo1 showing potentially protective effects in Aβ clearance but detrimental or adaptive changes in MS, while evidence for Piezo2 remains limited. Thus, Piezo channels represent potential mechanistic links between altered brain mechanics and neurodegeneration, but their therapeutic potential requires further validation.

4.2 Locomotor degenerative diseases

Locomotor degenerative diseases—musculoskeletal disorders of bone, joint, muscle, and peripheral nerves—are rising with population aging and impair motor function and quality of life in older adults [100]. Osteoarthritis and osteoporosis are common clinical manifestations, with comorbidities influencing their phenotype and progression. In line with the WHO Decade of Healthy Ageing 2021–2030 [101], understanding pathogenesis and developing effective interventions is essential to delay age-related musculoskeletal decline and promote healthy aging.

4.2.1 Osteoarthritis

Osteoarthritis (OA) is the most prevalent degenerative joint disease, affecting more than 500 million people worldwide and contributing substantially to motor impairment in older adults [102]. In aged bone, impaired matrix synthesis by osteocytes results in a poorly interconnected bone matrix that limits fluid strain transmission to osteocytes, thereby reducing their mechanosensitivity and force-generating capacity [6]. In cartilage, oxidative stress suppresses chondrocyte synthesis of ECM components, disrupting cartilage architecture and compromising its mechanical properties, which contributes to fissure formation, tissue fragmentation, and joint disorders such as OA [103]. Age-related ECM remodeling and excessive mechanical loading disrupt cartilage homeostasis and are associated with aberrant Piezo1 activation [104, 105]. Evidence from patients, animal models, and chondrocyte/synovial cell studies indicates that Piezo1 promotes OA progression by coupling mechanical stress to Ca^{2+}-dependent inflammatory, mitochondrial, and matrix-remodeling responses, including NF-κB/NLRP3, cGAS–STING, and PI3K/AKT/mTOR signaling [51, 52, 106-112]. Consistently, Piezo1 activation aggravates experimental OA, whereas its inhibition attenuates cartilage damage and osteophyte formation [52, 109]. In overloaded medial cartilage from genu varum patients undergoing knee arthroplasty, chondrocyte senescence was pronounced, with elevated P16, P21, and P53. Finite element analysis revealed that higher-stress regions showed greater erosion and higher miR-155-5p. In vitro, overloading specifically upregulated Piezo1 (not Piezo2) in human chondrocytes, while reducing GDF6, SMAD2/3, and their phosphorylated forms. Thus, supraphysiological loading drives human chondrocyte senescence and OA via Piezo1–miR-155-5p–GDF6–SMAD2/3 signaling [113].

Both Piezo1 and Piezo2 contribute to skeletal and cartilage homeostasis, as combined Piezo1/2 deficiency impairs cartilage growth and osteoblast differentiation in mice, indicating essential physiological functions during skeletal development [114]. In established OA, however, their roles appear context-dependent and complementary. Preclinical genetic studies suggest that Piezo1 primarily influences cartilage degradation and synovitis, whereas Piezo2 contributes more prominently to mechanical pain and skeletal maintenance; combined deficiency provides greater protection against cartilage damage, synovitis, and pain than loss of either channel alone [115]. Mechanistically, Piezo2 also mediates NGF-dependent sensitization of joint nociceptors, and pharmacological modulation of Piezo2 reduces mechanical hyperalgesia in mouse models, effects that are diminished by nociceptor-specific Piezo2 deletion [82, 116]. Thus, current

preclinical evidence suggests that coordinated modulation of Piezo1 and Piezo2 may target both structural progression and pain in OA, although their physiological roles necessitate careful consideration of cellular specificity and inhibition intensity (Table 1).

4.2.2 Osteoporosis/Bone loss

Osteoporosis, the common age-related loss of bone mass and microstructure, arises from a shift toward resorption and reduced mechanical responsiveness [22]. Age-associated deterioration of the bone matrix network contributes to bone loss and impaired mechanosensitivity. Osteocytes produce the mineralized bone matrix and establish an extensive interconnected lacunocanalicular system that facilitates nutrient exchange and enables efficient sensing of mechanical strain generated by fluid flow within bone [117]. However, reduced matrix synthesis by aged osteocytes progressively compromises the interconnectivity and mechanical stiffness of this matrix network during aging [118]. Piezo1 declines with age in cortical bone in mice and humans, and its loss in osteoblasts/osteocytes increases endocortical resorption by lowering OPG, exacerbating cortical bone loss [119]. Accumulating evidence from animal models and cellular studies suggests that Piezo1 generally supports bone homeostasis and protects against age- and unloading-related bone loss. Piezo1 deficiency in osteoblast-lineage cells and BMSCs impairs osteogenesis, promotes senescence and marrow adiposity, and reduces bone mass, partly through dysregulated YAP/Wnt and Ca^{2+}-dependent metabolic signaling [22, 120-125]. Consistently, Piezo1 activation by Yoda1 or fluid shear stress enhances osteogenesis, mitochondrial function, and osteocyte survival, with beneficial effects reported in experimental models of disuse, aging, ovariectomy, and glucocorticoid-induced bone loss [123, 124, 126]. However, these findings are predominantly preclinical, and the safety and efficacy of sustained Piezo1 activation for osteoporosis remain to be established.

In humans, mutations in the Piezo2 gene have been found to cause skeletal abnormalities, including scoliosis and hip dysplasia [127]. Knocking out the Piezo2 gene alone does not result in detectable skeletal phenotypes in mice; however, more severe skeletal defects are observed in Piezo1/Piezo2 double-knockout mice [114]. This suggests that Piezo2 may be involved in skeletal development, and its non-essential role in the single-gene knockout model is likely due to compensatory mechanisms mediated by Piezo1 (Table 1).

4.2.3 Intervertebral disc degeneration and senescence of nucleus pulposus cells

Intervertebral disc degeneration (IVDD) is a common spinal condition caused by aging, mechanical stress, and lifestyle factors, and typically presents as lower back pain, herniated discs, and spinal instability [128]. It begins with pathological changes in the NP, particularly a decrease in type II collagen and an increase in type I collagen, which affect the annulus fibrosus (AF) and the cartilaginous endplates (CEP) [129]. In human IVD tissue, aging leads to a decrease in proteoglycan content, reduced water retention, impaired biomechanics, and vascular calcification—all of which compromise the disc's ability to withstand mechanical loads [130]. Pathological mechanical stress worsens these changes by boosting inflammation, ECM degradation and cell death [131]. Evidence from human tissues, aged/instability models, and cellular studies shows that Piezo1 is increased or activated in degenerated NP and CEP, whereas genetic or pharmacological inhibition attenuates disc degeneration, matrix loss, and cell death [132, 133]. Mechanistically, Piezo1-mediated Ca^{2+} influx activates distinct downstream pathways, including NF-κB/NLRP3 signaling, Ca^{2+}/F-actin/YAP, and Ca^{2+}/CaMKII/Drp1, thereby promoting inflammation, senescence, mitochondrial fission, and apoptosis [133-139]. In AF cells, however, low-strain cyclic stretch may activate Piezo1–calcineurin signaling to suppress BMP-dependent osteogenesis and maintain tissue homeostasis [135], suggesting that Piezo1 effects are context- and load-dependent. In human NP tissues, matrix stiffening has also been linked to Piezo1-dependent Ca^{2+}–ERK1/2–Drp1 signaling and mitochondrial apoptosis [138]. Because the CEP is essential for nutrient diffusion and disc homeostasis [140, 141], its Piezo1 activation may further aggravate IVDD through Ca^{2+}/CaMKII/Drp1-mediated mitochondrial dysfunction and YAP–TEAD/NLRP3-dependent inflammation and matrix degradation [107, 139]. Collectively, Piezo1 appears to contribute to IVDD by linking abnormal mechanical stress to inflammatory, metabolic, and mitochondrial dysfunction (Table 1).

Collectively, Piezo channels appear to play context-dependent roles in locomotor degenerative diseases by linking altered mechanical stress to inflammation, senescence, mitochondrial dysfunction, and tissue remodeling. Piezo1 generally promotes pathological changes in OA and IVDD, but supports bone homeostasis and osteogenesis, whereas Piezo2 contributes to skeletal maintenance and joint pain. These findings highlight the tissue- and cell-specific functions of Piezo channels and suggest that therapeutic targeting should consider their distinct physiological and pathological roles.

4.3 Cardiovascular and cerebrovascular diseases

Cardiovascular and cerebrovascular diseases are systemic

vascular disorders, with population aging driving their rising mortality and making them the leading health threat in adults aged ≥60 [142]. In mammals, Piezo channels show distinct tissue distribution and regulate key physiological processes [19]. Recent studies have revealed their roles in cardiovascular/cerebrovascular pathogenesis; this section reviews current findings on Piezo proteins in major vascular diseases, focusing on age-related mechanisms and potential anti-aging strategies.

4.3.1 Atherosclerosis

Atherosclerosis (AS) is a major global cardiovascular disease caused by arterial lipid–fibrous accumulation and can lead to myocardial infarction and stroke [143]. Aging alters arterial biomechanics by promoting arterial stiffening and impairing contractile function, thereby reducing the ability of arteries to buffer pulsatile blood flow. These changes reflect age-related deterioration of the structure and function of the arterial wall's principal load-bearing components. Because elastin undergoes progressive fragmentation and its de novo synthesis largely ceases after adulthood, elastin damage accumulates with age. Although increased collagen deposition partially compensates for the loss of elastin integrity, substitution of compliant elastin with stiffer collagen progressively increases arterial wall stiffness [144]. Its pathogenesis centers on endothelial dysfunction driven by oxidative stress and inflammation [145]. Evidence from animal and cellular models supports a pro-atherogenic role of Piezo1 under disturbed flow. In atherosclerotic endothelium, aberrant Piezo1 activation by oscillatory shear stress (OSS) or oxidized low-density lipoprotein (oxLDL) increases Ca^{2+} influx and triggers CaMKII/FAK/Src–YAP/TAZ and NF-κB signaling, promoting endothelial inflammation, impaired autophagy, and plaque formation [54, 146, 147]. Mechanistically, Piezo1 also induces ETS1/c-JUN–KDM5B-dependent epigenetic remodeling, further amplifying vascular inflammation [148]. Conversely, Piezo1 inhibition or endothelial deletion attenuates these pathological responses and AS in experimental models [54, 148, 149]. Thus, current evidence indicates that Piezo1 links disturbed mechanical forces to vascular inflammation.

In addition, hemodynamic shear stress regulates vascular homeostasis through endothelial Piezo1 signaling, which may promote anti-ferroptotic and anti-inflammatory responses via the BHLHE40-SLC7A11 axis and limit oxLDL uptake through SIRT4 [150-152]. Conversely, oxLDL activates macrophage Piezo1 to enhance Ca^{2+} signaling and lipid uptake, while 7-ketocholesterol generated during LDL oxidation may further enhance Piezo1 expression and mechanogating [153, 154]. These findings suggest that Piezo1 integrates hemodynamic and lipid-related cues to regulate atherosclerotic progression (Table 1).

4.3.2 Calcific Aortic Valve Disease

Calcific Aortic Valve Disease (CAVD) is the most prevalent valvular heart condition, marked by advancing calcification of the aortic valve that results in aortic stenosis and a range of cardiovascular complications [155]. In healthy aortic valves, the ECM exhibits an orderly arrangement. As CAVD progresses, the ECM undergoes substantial remodeling in its structure, composition, and biomechanical properties. Specifically, abnormal collagen deposition, reduced and fragmented elastin, along with increased proteoglycans and glycosaminoglycans, collectively lead to valve thickening, heightened ECM stiffness, and decreased valve pliability [156, 157]. As the predominant cell type in the aortic valve, valvular interstitial cells (VICs) maintain valve homeostasis by participating in the renewal and remodeling of the ECM [158]. VICs express mechanosensitive proteins and serve as "mechanosensors" that detect a variety of mechanical cues, including shear stress, tension, pressure, and matrix stiffness [159]. Increased matrix stiffness in calcified aortic valves upregulates Piezo1, promoting ECM remodeling and osteogenic differentiation of VICs. Piezo1 silencing or knockdown reduces COL4A3 expression, prevents VIC osteogenesis, and ameliorates valve calcification in mice, suggesting a Piezo1-mediated feedback loop involving Wnt signaling in CAVD progression [160]. Mechanistically, Piezo1 activation by Yoda1 or oscillatory stress triggers Ca^{2+}-dependent YAP activation, which upregulates GLS1-mediated glutaminolysis and promotes osteogenic differentiation of valve interstitial cells via histone acetylation of the RUNX2 promoter. Inhibiting Piezo1 or GLS1 mitigates aortic valve lesions in stenosis models [161] (Table 1).

4.3.3 Heart failure

Heart failure (HF) is the common clinical outcome of various diseases and a leading cause of morbidity and mortality worldwide; driven by an aging population and unhealthy lifestyles, its prevalence continues to rise [162]. Functional remodeling in HF is frequently accompanied by increased myocardial passive stiffness, particularly in HF with preserved ejection fraction (HFpEF) [163]. Age-related alterations in cardiac ECM composition and crosslinking disrupt cardiomyocyte function and mechanical properties, thereby contributing to the development of cardiac fibrosis and ultimately HF [5]. Piezo1 plays a key regulatory role in the

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pathophysiological processes of HF. Elevated levels of the Piezo1 protein have been observed in both humans and mice with HF [164]. Blythe et al. found that Piezo1 activation in human and mouse cardiac fibroblasts is coupled with p38α MAPK pathway activation and IL-6 secretion. Increased atrial fibroblasts or cardiac stretch activates Piezo1 to elevate Ca^{2+} influx, triggering inflammation, fibroblast proliferation and myocardial fibrosis [165]. Under pressure overload, Piezo1 initiates the CaMKII–HDAC4–MEF2 hypertrophic signaling cascade to induce left ventricular hypertrophy [166]. CM-specific deletion of Piezo1 in adult mice blocks CaMKII activation and attenuates cardiac hypertrophy [167]. Physiologically appropriate Piezo1 expression in cardiomyocytes maintains homeostasis, while its overexpression causes cardiac injury.

Compared with healthy individuals, heart failure patients exhibit significantly higher myocardial Piezo2 mRNA alongside elevated TET3 and myofibroblast markers. Increased Piezo2 correlates with reduced left ventricular ejection fraction (LVEF) and impaired cardiac function, implying its potential diagnostic value, which requires validation in larger clinical cohorts [168]. Mechanistically, TET3 promotes cardiac fibroblast activation and fibrosis in mice via upregulating the mechanosensor Piezo2; pharmacological degradation of TET3 or Piezo2 inhibition attenuates cardiac fibrosis and restores heart function [168] (Table 1).

4.3.4 Myocardial infarction

Myocardial infarction (MI) is myocardial cell death from prolonged ischemia and a leading cause of morbidity and mortality [169]. Post-MI cardiomyocyte loss drives adverse left-ventricular remodeling and HF [170]. Following MI, initial structural and electrical remodeling serves as a compensatory response to preserve cardiac function. However, persistent ischemia, sustained sympathetic activation, and chronic inflammation progressively promote ventricular dilation and fibrosis, resulting in adverse changes in cardiac mechanical properties, including increased end-diastolic pressure [163]. Piezo1 mRNA expression was elevated in human failing hearts with dilated cardiomyopathy, whereas Piezo2 and other key ion channels showed no significant changes [171]. Accumulating evidence suggests a preferential role of Piezo1 in pathological cardiac remodeling. Piezo1 is elevated in failing human hearts, whereas Piezo2 remains unchanged [171]. In mice with MI, Piezo1 promotes adverse remodeling through distinct cell-specific mechanisms, including Ca^{2+}-dependent CaMKII/calpain–RyR2 signaling in cardiomyocytes, IL-6-mediated neurogenic inflammation in sensory neurons, and ferroptosis and impaired efferocytosis in macrophages [172, 173]. These pathways converge on Ca^{2+}, inflammatory, and oxidative stress signaling, with Piezo1–Ca^{2+}–ROS feedback further amplifying ischemic injury [164]. However, the cell-dependent effects of Piezo1 highlight the need for tissue- or cell-specific rather than systemic targeting (Table 1).

4.3.5 Stroke

Stroke is the second leading cause of death, the third leading cause of disability, and a major cause of dementia globally [174]. Neuroinflammation represents a key pathological feature of ischemic stroke and intracerebral hemorrhage (ICH), influencing both the progression of brain injury and subsequent repair processes. In the early phase of ischemic stroke and ICH, immune cells participate in ECM deposition and remodeling, thereby regulating processes such as BBB integrity and cellular stability [175]. Evidence from cellular and animal models suggests that Piezo1 contributes to ischemic stroke injury through Ca^{2+} signaling. Cerebral ischemia–reperfusion upregulates Piezo1, promoting neuronal apoptosis and autophagy through the Ca^{2+}–AMPK–mTOR axis, while its silencing is neuroprotective [176]. In the neurovascular unit, endothelial Piezo1 aggravates BBB disruption, oxidative stress, and inflammation via Ca^{2+}/CaMKII–Nrf2 signaling, whereas its deletion preserves BBB integrity [177]. Increased post-stroke scar stiffness may further activate astrocytic Piezo1–Ca^{2+}–Wnt7b signaling, promoting fibrotic scar formation, while Piezo1 inhibition reduces scar stiffness and improves neuroregeneration and motor recovery [178]. Piezo1 deletion also attenuates astrocyte activation and MMP expression, strengthens tight-junction integrity, and reduces ischemia-associated cognitive impairment [179]. Overall, current evidence is predominantly preclinical, supporting Piezo1 as a potential mechanosensitive mediator of neuronal, vascular, and glial responses after stroke, although its cell-specific functions and therapeutic window remain unresolved.

ICH is a devastating stroke subtype with high mortality and disability and few effective treatments or reliable acute diagnostics [180]. Neuronal Piezo1 protein expression was markedly increased 24 h after ICH in vivo in both humans and mice [181]. In a mouse autologous-blood ICH model (right basal ganglia), Piezo1 rose within 48 h mainly in oligodendrocytes, and the Piezo1 inhibitor Dooku1 reduced edema, myelin loss, oligodendrocyte apoptosis and improved neurologic function by lowering ER stress and apoptosis via PERK-ATF4-CHOP and IRE1 pathways [182]. Another mouse study showed the Piezo1 blocker GsMTx4 (alone or with mannitol) decreased Piezo1 and AQP4, increased Bcl2, preserved neurons and cerebral blood flow, reduced

edema and serum IL-6, and reversed deficits at 24 h, whereas the agonist Yoda-1 had opposite effects [181].

At the same time, Piezo2 also plays a significant role in brain damage caused by ICH. In a rat ICH model with controlled mass effect, increased mass effect upregulated Piezo2 expression along with iron uptake proteins (DMT1, TfR) and ferroptosis, which were reversed by the pERK1/2 inhibitor PD98059 [183]. These findings indicate that mass effect may exacerbate iron overload and ferroptosis after ICH, partly through Piezo-2-mediated mechanisms (Table 1).

Collectively, Piezo1 exhibits relatively broad and context-dependent effects across various vascular and cardiac/cerebral injury models, whereas evidence for Piezo2 remains relatively limited, mainly involving cardiac fibrosis and ICH. Therefore, targeting Piezo channels may hold therapeutic potential; however, their cell-specific effects highlight the need for further mechanistic and in vivo validation.

4.4 Fibrosis in the Aging Process

Fibrosis is a chronic pathological response marked by excessive ECM deposition, which disrupts normal structure and function in vital organs such as the heart, lungs, liver, and kidneys, potentially leading to progressive dysfunction and, in severe cases, death [184]. Elevated ECM stiffness, a characteristic feature of fibrotic tissues caused by excessive collagen and other ECM deposition, promotes fibroblast activation and proliferation, thereby establishing a positive feedback loop that sustains inflammation and fibrosis [185]. Abnormal ECM deposition increases mechanical stiffness, which primarily triggers Piezo channel activation during fibrosis across various organs. Piezo1 may link age-related mechanical stress to tissue fibrosis and stiffening through Ca^{2+}-dependent signaling. Evidence from aged animals, simulated-microgravity models, and peripheral nerve injury models indicates that Piezo1 activation promotes ECM deposition, cellular senescence, and tissue stiffness [18, 186-189]. Mechanistically, Piezo1 engages tissue-specific pathways, including miR-582-5p/PTEN–PI3K/Akt in vascular smooth muscle, Wnt/β-catenin in the aged uterus, and TGF-β-associated senescence signaling in Schwann cells, thereby promoting fibrotic remodeling [187-189]. Notably, vascular smooth muscle–specific Piezo1 deletion or inhibition of downstream miR-582-5p attenuates fibrosis and stiffness in aged or mechanically stressed rats [187], supporting a role for Piezo1 in mechanically driven fibrotic remodeling.

Piezo2 may couple ECM stiffening to fibroblast activation and fibrosis. Evidence from human fibrotic tissues and mouse models shows that Piezo2 is enriched or upregulated in profibrotic fibroblasts, while fibroblast-specific deletion or pharmacological blockade attenuates myofibroblast activation and tissue fibrosis [70, 186]. Mechanistically, Piezo2 signaling is regulated by m^6A-dependent YTHDF1-mediated translation and contributes to stiffness-responsive profibrotic remodeling, whereas its inhibition reduces these responses [70, 190]. In fibroblasts, Piezo2 is implicated in the regulation of cellular senescence, as TGM2 promotes senescence partly by repressing Piezo2, whereas Piezo2 knockdown counteracts the inhibitory effects of TGM2 suppression on cGAS–STING signaling and cellular senescence [64]. Collectively, current human and experimental evidence suggests that Piezo2 participates in mechanosensitive regulation of fibrosis and cellular senescence (Table 1).

Collectively, emerging evidence suggests that Piezo1 and Piezo2 may contribute to fibrosis by linking ECM stiffening to fibroblast activation, inflammation, senescence, and excessive matrix deposition. Piezo1 appears to promote fibrotic remodeling across multiple organs, whereas Piezo2 is increasingly implicated in fibroblast activation and myofibroblast differentiation in cardiac and pulmonary fibrosis.

4.5 Other age-related conditions

The number of people living with chronic diseases is continuously increasing, largely driven by population aging and the rising incidence of diabetes [191]. Among older adults, medical expenses for chronic conditions account for a disproportionately high share. Prioritizing research and quality improvement in healthcare for this specific population holds promise for enhancing service delivery and reducing costs. The preceding sections have described the roles of Piezo proteins in neurodegenerative diseases, movement-related degenerative diseases, fibrosis, and cardiovascular and cerebrovascular disorders. Notably, several other age-related diseases also warrant significant research attention, including but not limited to diabetes and its complications, hypertension, and age-related skin changes.

4.5.1 Diabetes

The global prevalence of type 1 and type 2 diabetes mellitus (T1DM and T2DM) continues to rise. Complications of diabetes, including neuropathy, cardiovascular changes, and kidney disease, are the leading causes of mortality and morbidity among people with diabetes, posing a significant burden on global public health [192]. In T2DM, excessive ECM deposition, particularly of type I and type III collagen, fibronectin, and hyaluronan, increases tissue stiffness [38]. Similarly, marked accumulation of hyaluronan within and around

the islets has been observed during early T1DM, potentially contributing to elevated local tissue stiffness and the islet dysfunction characteristic of preclinical T1DM [193]. Human islet samples reveal elevated Piezo1 expression in islets from type-2-diabetes patients [194]. Hyperglycemia has been reported to enhance PIEZO1 expression and activity in various cell types, including neurons, microglia, and endothelial cells [194, 195]. Under diabetic conditions, aberrant PIEZO1 activation contributes to vascular and neural dysfunction. In pancreatic β-cells, PIEZO1 regulates glucose-stimulated insulin secretion through calcium-dependent exocytosis; however, chronic hyperglycemia may impair PIEZO1 responsiveness or disrupt its coupling with the exocytotic machinery, leading to reduced insulin release and β-cell dysfunction [194]. Moreover, dysregulated endothelial PIEZO1 signaling promotes vascular impairment by reducing vasodilation and nitric oxide (NO) production, thereby contributing to diabetic vascular complications [196]. In the nervous system, excessive PIEZO1 activation increases cellular susceptibility to hyperglycemic stress, resulting in calcium overload, mitochondrial dysfunction, neurotoxicity, and enhanced inflammatory responses [197, 198]. Collectively, these findings suggest that PIEZO1 dysregulation may contribute to the progression of diabetic vascular and neurological complications.

Compared with Piezo1, Piezo2 is less studied in diabetes but appears involved in diabetic complications. In Diabetic kidney disease (DKD), Piezo2 is upregulated in mesangial cells and interstitium, correlating with increased fibronectin and matrix accumulation; Angiotensin II receptor blocker treatment reduces Piezo2 and fibronectin, and Piezo2 overexpression increases fibronectin in vitro, implicating Piezo2 in glomerular sclerosis [199]. In diabetic gastroparesis, tuina improved gastric emptying, reduced tissue damage, and increased ileal Piezo2, 5-HT4R and 5-HT, suggesting a protective Piezo2/5-HT mechanism [200]. In Diabetic distal symmetric polyneuropathy, patients show microvascular remodeling with painful cases having weak Piezo1 but elevated Piezo2, linking vessel changes and Piezo subtype shifts to neuropathic pain [201]. Overall, Piezo2 may have potential roles in diabetic complications, but its therapeutic potential remains unclear (Table 1).

4.5.2 Hypertension

Hypertension, a leading risk factor for cardiovascular diseases such as stroke and coronary heart disease, can arise from impaired vasodilation [202]. Pathological ECM remodeling can disrupt vascular function by altering endothelial signaling, vascular smooth muscle cell responsiveness, and the mechanical interactions between these cells and the surrounding ECM. Piezo1 is a key molecule enabling the vascular wall to sense blood pressure fluctuations. Elevated blood pressure increases the mechanical stress exerted on the vascular wall, opening Piezo1 channels and resulting in substantial Ca^{2+} influx. This effect directly triggers the contraction of VSMCs and raises vascular tension. Meanwhile, it impairs the normal physiological functions of VSMCs, promotes vascular remodeling, and accelerates the progression of hypertension [203, 204]. Up-regulated Piezo1 expression can be detected in animal models of hypertension. At the molecular level, Piezo1 activates downstream pathways including AKT, ERK, and CaMKII via Ca^{2+}-dependent signaling, mediating the proliferation, migration and phenotypic switching of VSMCs [205, 206]. In addition, Piezo1 activation stimulates endothelial cells to release inflammatory mediators and induces oxidative stress, which disrupts endothelial structural integrity and ultimately forms a vicious cycle of "endothelial injury-vascular remodeling-elevated blood pressure" [206]. Existing studies have verified that Piezo1 inhibitors block Ca^{2+} influx in VSMCs, reduce vascular tension and restore vascular function [207, 208].

Piezo1 and Piezo2 both participate in blood-pressure regulation, but their roles and expression patterns vary across tissues and pathological states. Genetic and optogenetic evidence shows that Piezo2 is the predominant mechanosensor in nodose ganglion (NG) baroreceptor neurons and aortic afferents, where its activation evokes the baroreflex; notably, Piezo2 is downregulated in hypertension, and Nedd4-2-mediated degradation further impairs baroreflex function and increases blood pressure [209, 210]. In hypertensive nephropathy, however, Piezo2 is upregulated in renal mesangial, renin-producing, and perivascular cells and is associated with renal injury [211]. Consistent with a more complex interaction between the two channels, hypertensive rats show increased Piezo1 and Piezo2 in the left ventricle, whereas Piezo1 decreases in the aorta and NG and Piezo2 increases in the corresponding sites [212]. Yoda1 activation of Piezo1 in NG lowers blood pressure and enhances aortic depressor nerve and nucleus tractus solitarius neuronal activity, suggesting that Piezo1 and Piezo2 may act through partially overlapping, compensatory, and synergistic mechanisms in cardiovascular mechanotransduction [212]. Thus, Piezo2 appears particularly important for baroreceptor sensing, while Piezo1 may interact with Piezo2 in a tissue- and circuit-dependent manner (Table 1).

4.5.3 Age-related skin changes

Skin aging results from multiple factors, featuring a gradual decline in both function and regenerative capacity

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[213]. Fibroblasts are abundant in the skin and tissue interstitium, where they synthesize substantial amounts of ECM to support neighboring functional cells. Age-related mechanical alterations in human dermal fibroblasts are associated with changes in the organization and density of ECM collagen and elastin [214]. In addition, changes in matrix metallopeptidases (MMPs), collagen cross-linking, and matrix viscoelasticity diminish the mechanical support and cues received by aging dermal fibroblasts [14, 214]. It is well established that ECM stiffness changes with age, leading to decreased skin elasticity and wrinkle formation [215]. Skin vasculature atrophy with age causes dermal stiffening, which activates Piezo1 in interfollicular epidermal stem cells, leading to prolonged Ca^{2+} influx, increased differentiation, and hemidesmosome fragility. Epidermal Piezo1 deletion ameliorates this dysregulation, while dermal vascular restoration softens the matrix and rescues stem cell function [216]. Piezo1 may contribute to skin rejuvenation by coupling mechanical or biomaterial-derived stimuli to regenerative responses in aged skin. In aged mouse models, Poly L-lactic acid (PLLA) and radiofrequency activate Piezo1, promoting Ca^{2+}-dependent ERK/AKT/mTOR signaling, collagen production, and restoration of dermal-epidermal junction (DEJ) components, including collagen XVII and collagen IV; these effects are attenuated by Piezo1 blockade [217, 218]. Beyond the DEJ, Piezo1 activation in senescent macrophages promotes M2 polarization and growth-factor secretion, including HGF/IGF-1 and FGF2, thereby enhancing ERK-dependent HFSC proliferation and adipose-derived stem cell proliferation/adipogenesis, respectively, with improvements in hair growth and subcutaneous adipose tissue thickness in aged mice [219, 220]. Collectively, preclinical mouse evidence suggests that Piezo1 may support age-related skin and appendage regeneration through Ca^{2+}-dependent signaling and macrophage–stem cell crosstalk.

Aging impairs the somatosensory system at all levels from peripheral receptors to the cortex [221]. In skin, Meissner and Merkel cells show loss, morphological changes, reduced Piezo2 and diminished BDNF-TrkB signaling (Pacinian corpuscles are less affected), may collectively contribute to tactile decline [222]. Loss of Merkel cells and their Piezo2 channel in aged or dry mouse skin is associated with mechanical itch (alloknesis), whereas chemogenetic activation of Merkel cells reduces this response [223], raising the possibility that Piezo2-expressing cutaneous touch receptors may contribute to the suppression of pathological itch (Table 1).

Collectively, Piezo1 appears to play important roles in tissue mechanotransduction and disease-associated remodeling, whereas Piezo2 remains less well studied and appears to have more specialized roles in baroreception, diabetic complications, and cutaneous mechanosensation. Both subtypes may exert compensatory or synergistic effects depending on cell type, mechanical environment, and disease stage.

5. Piezo as a potential therapeutic target for age-related diseases

Piezo channels have attracted increasing interest as potential targets in aging and age-related diseases; however, Piezo-targeted interventions remain predominantly preclinical, with evidence derived mainly from cellular, ex vivo, and animal models, while clinically validated pharmacological therapies have yet to be established. Current studies have explored both activation and inhibition of Piezo channels, as well as emerging approaches including exercise, ultrasound, nanotechnology, dietary fatty acids, and natural compounds. Although these interventions show beneficial effects in experimental models, their specificity, efficacy, safety, and translational potential require further validation.

5.1 Direct pharmacological modulators of Piezo channels

Although Piezo channels are mainly mechanically gated, small molecules can modulate them: Yoda1 and its derivatives, as well as Jedi1/2, are among the best-characterized chemical activators of Piezo1 [224, 225]. Yoda1 was identified as the first small-molecule Piezo1 activator, altering mechanical sensitivity and inactivation kinetics and potentiating tension-induced activation in a voltage- and temperature-dependent manner [224, 225]. Systemically, Yoda1 improves blood perfusion in AD models [226]; in human iMGL cells and 5xFAD mice it enhances microglial migration, Aβ42 phagocytosis, lysosomal function, increases Iba1+ microglia and reduces cortical/hippocampal plaques [227]. Yoda1 restores cerebrospinal fluid flow, lowers intracranial pressure and promotes meningeal lymphangiogenesis in craniosynostosis and aged mice [228]. In bone, Yoda1 combined with moderate loading protects against age-related cortical/trabecular loss better than either alone but cannot rescue doxorubicin-induced damage [229]; Piezo1 activation in pre-osteoclasts suppresses RANKL-driven osteoclastogenesis via a Ca2+ -independent PP2A-Akt-NFATc1 pathway, preventing inflammatory bone loss [230]. However, in breast cancer-induced osteolysis Yoda1 alone worsened bone loss whereas combined loading had modest benefits, cautioning against monotherapy in metastatic settings [231]. Finally, Piezo1 is upregulated in atherosclerotic

plaques and Yoda1 promotes foam cell apoptosis/phagocytosis and reduces lesions in ApoE−/− mice; it also counters low-shear–induced NETosis/ROS via restored Ca2+ influx [232, 233]. Replacing the pyrazine group of Yoda1 with 4-benzoic acid yields Yoda2 (KC159), and its potassium salt KC289 exhibits greater potency than Yoda1, with EC50 values of 280 nM and 150 nM, respectively, on mouse Piezo1 [234]. As age increases, bone mechanosensitivity declines and its adaptive capacity becomes limited. In 22-month-old mice, a 2-week tibial loading combined with injection of the Piezo1 agonist Yoda2 synergistically improves cortical bone parameters; Yoda2 activates Piezo1 in osteocytes, counteracting age-related bone loss [235].

In addition to Yoda1/2, high-throughput screening has identified Jedi1 and Jedi2 as specific pharmacological activators of Piezo1 [236]. Although structurally distinct from Yoda1, both Jedi compounds dose-dependently activate human and mouse Piezo1 channels [236]. Pharmacological modulation of Piezo1 using the activators Yoda1 or Jedi1/2 alters ECM deposition and kidney function in animal models of renal fibrosis [237]. Furthermore, researchers synthesized 12 brain-targeted conjugates of the activators Jedi1 and Jedi2 using L-type amino acid transporter 1. These novel compounds showed improved transport into mouse BV2 microglia cells and greater Piezo1 activation than their parent compounds, along with enhanced brain delivery and reduced peripheral distribution [238].

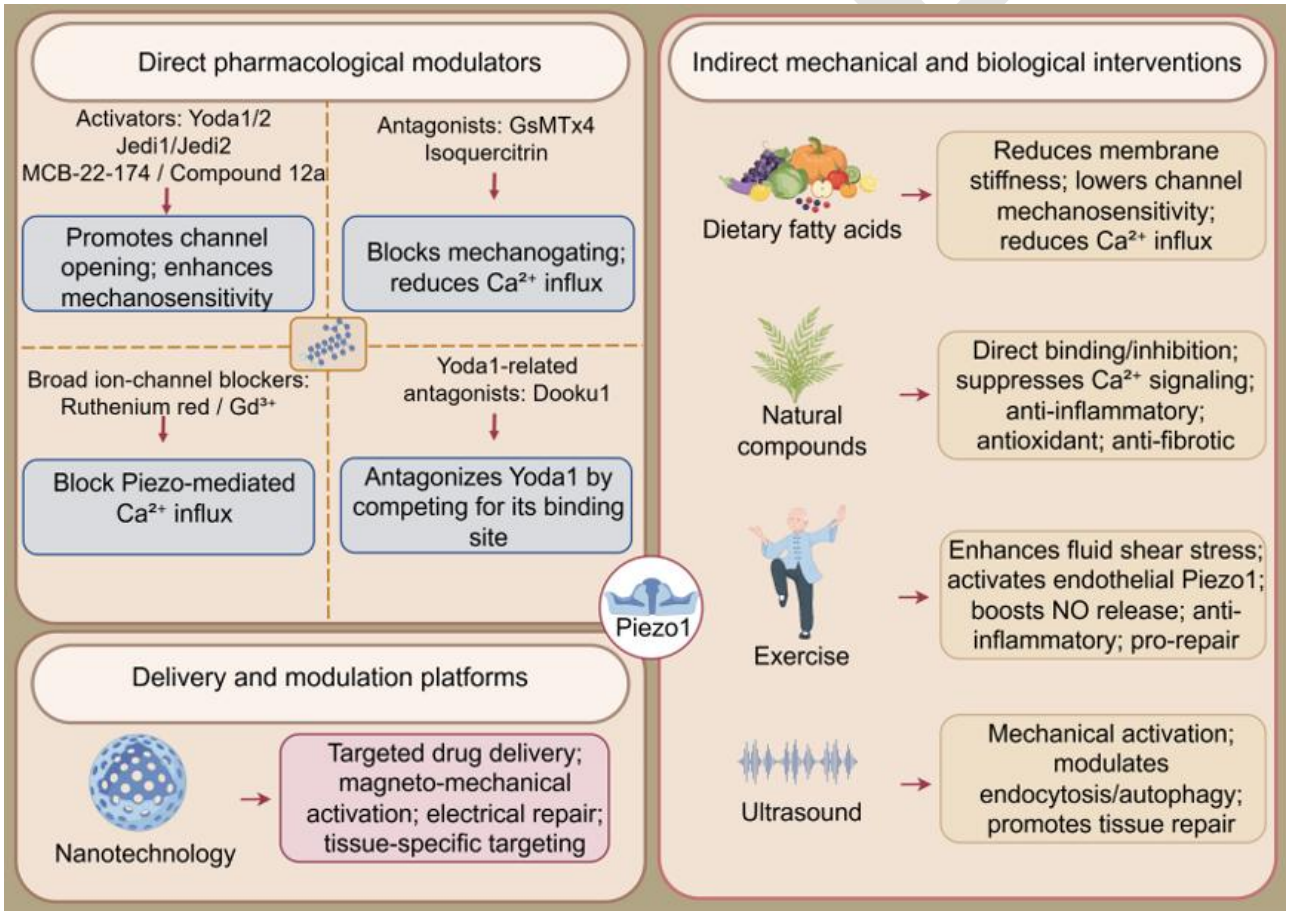


Figure 3. Pharmacological and non-pharmacological strategies targeting Piezo1 signaling. Potential therapeutic approaches targeting Piezo1 include direct pharmacological modulation, lifestyle-associated mechanical interventions, and advanced delivery systems. Small molecules, natural compounds, dietary fatty acids, exercise, ultrasound stimulation, and nanotechnology-based approaches may regulate Piezo1-mediated Ca^{2+} signaling through modulation of channel activity, mechanical inputs, or drug delivery efficiency. Current evidence from preclinical studies suggests potential anti-inflammatory, antioxidant, anti-fibrotic, tissue-reparative, and metabolic benefits; however, their clinical applicability requires further validation. Abbreviations: Ca^{2+}, calcium ion; Gd^{3+}, gadolinium ion; NO, nitric oxide.

The novel agonist MCB-22-174 is more potent than Yoda1, promotes BMSC proliferation and osteogenesis via Ca2+/ERK/CaMKII, and alleviates disuse osteoporosis (DOP) in vivo without obvious toxicity

[239]. A deuterated (thiadiazol-2-yl) pyrazine derivative, compound 12a (EC50 = 2.21 μM, >20-fold more potent than Yoda1), activates Ca2+/Erk signaling in MSCs to promote osteogenesis and mitigate DOP in rats [240].

Yoda1-related antagonists represent a distinct pharmacological category. Dooku1, a Yoda1 analog, lacks intrinsic PAM activity but antagonizes Yoda1 by competing for its binding site, blocking Yoda1-triggered Ca2+ entry and attenuating Yoda1-induced aortic diastole and medial arterial calcification in mouse [241, 242].

Several Piezo1 blockers have been reported; notably the spider venom peptide GsMTx4 selectively antagonizes cationic mechanosensitive channels, inhibiting Piezo1 and Piezo2 [243]. Its likely mechanism is insertion into the expanding membrane outer leaflet, reducing the effective mechanical stimulus for channel gating [243]. GsMTx4 reverses Yoda1-induced apoptosis, mitochondrial dysfunction and fibrosis in renal cells [244], and in OA models increases GPX4, attenuates ferroptosis, inhibits chondrocyte apoptosis, promotes cartilage matrix via the Piezo1/calcineurin/NFAT1 axis, and relieves mechanical pain [245-247]. It also prevents compression-induced ECM disruption and apoptosis in NP cells and limits IL-1β-driven disc degeneration ex vivo [132] and protects AF cells from stretch-induced apoptosis similarly to Piezo1 knockdown [248]. In vivo, GsMTx4 improves cognition, cerebral edema and BBB integrity in chronic cerebral hypoperfusion via NLRP3 inhibition [249], reduces vitamin D–induced aortic calcification and AS and suppresses flow-induced endothelial ICAM-1/VCAM-1 expression to slow plaque progression [146, 250]. GsMTx4 also protects against cerebral ischemia/reperfusion and OGD/R injury by blocking Piezo1-driven Ca2+/calpain signaling (contrasting with Yoda1 which worsens injury) [251], inhibits hypertension-induced platelet activation and thrombosis [252], and markedly reduces myocardial I/R-induced dysfunction, infarct size, cell death, oxidative stress, inflammation and PANoptosis-related mediators [253]. These findings support a potential role for Piezo1 inhibition in several experimental disease models.

Isoquercitrin (ISQ) has also been reported as a negative allosteric Piezo1 modulator. In rat models of hydrocephalus and ICH, ISQ reduced Yoda1/Jedi1-induced Ca2+ overload, downregulated Piezo1 and NLRP3, suppressed caspase-1, p-p65, and IL-1β, and reduced neuronal apoptosis through the Piezo1/NLRP3 pathway [254].

Ruthenium red (RR) and gadolinium ions (Gd3+) are broad-spectrum blockers of mechanosensitive ion channels and can inhibit Piezo-mediated Ca2+ influx. However, their substantial off-target activities preclude their use as Piezo-selective inhibitors. In cardiac fibroblasts, RR and Gd3+ have been reported to reduce IL-6 production and pathological remodeling [255]. These compounds should therefore be regarded primarily as experimental channel blockers rather than selective Piezo-targeted therapeutic agents (Fig. 3; Table 2).

Table 2. Current therapeutic strategies targeting Piezo channels: mechanisms, preclinical evidence, limitations, and translational potential.

Therapeutic intervention	Selectivity	Main mechanism of Piezo modulation	Evidence level	Key limitations	Translational progress	Refs
Direct pharmacological modulators of Piezo channels						
Yoda1	Piezo1 agonist	Enhances Piezo1 mechanosensitivity and modifies inactivation kinetics	In vitro Cellular; animal studies	Safety and dosing remain unclear	Preclinical tool compound; no clinical application	[226-233]
Yoda2	Piezo1 agonist; higher potency than Yoda1	Activates Piezo1 and enhances mechanical signaling	In vitro Cellular; animal studies	Long-term efficacy and safety remain unknown	Early preclinical stage	[234, 235]
Jedi1/Jedi2	Piezo1 agonists; selectivity requires further validation	Dose-dependent activation of human and mouse Piezo1	In vitro Cellular; animal studies	Therapeutic efficacy, safety and in vivo target engagement remain unestablished	Preclinical	[236-238]
MCB-22-174 / Compound 12a	Piezo1 agonists; higher potency than Yoda1	Piezo1→Ca^{2+}/ERK/CaMK II signaling	In vitro Cellular studies	Limited disease models and insufficient pharmacological/safety characterization	Early preclinical	[239, 240]
Dooku1	Yoda1-related Piezo1 antagonist	Competes at the Yoda1-binding site and blocks	In vitro Cellular;	Broader therapeutic utility remains unclear	Experimental antagonist	[241, 242]

		Yoda1-induced Ca^{2+} entry	ex vivo; animal studies			
GsMTx4	Inhibits Piezo1 and Piezo2; not subtype-selective	Inserts into the membrane outer leaflet and reduces the effective mechanical stimulus for channel gating	In vitro Cellular; ex vivo; animal studies	Poor Piezo subtype selectivity; peptide pharmacokinetics, tissue distribution and long-term safety remain unresolved	Widely used preclinically; no established clinical translation	[132, 146, 243-253]
Isoquercitrin (ISQ)	Negative allosteric Piezo1 modulator; selectivity requires validation	Reduces Yoda1/Jedi1-induced Ca^{2+} overload and suppresses Piezo1/NLRP3 signaling	In vitro Cellular; animal studies	Direct target engagement and in vivo selectivity require further validation	Preclinical	[254]
Ruthenium red / Gd^{3+}	Non-selective mechanosensitive channel blockers	Block Piezo-mediated Ca^{2+} influx	Mainly cellular	Substantial off-target effects; unsuitable as Piezo-selective therapeutics	Mainly experimental tools	[255]
Indirect mechanical and biological interventions						
Natural compounds	Generally limited Piezo1 selectivity	Modulate Piezo1-Ca^{2+} signaling and downstream calcineurin/TFEB, PI3K-AKT, NF-κB/NLRP3 and YAP/JNK pathways	In vitro Cellular; animal studies	Multi-target effects; limited evidence for direct/selective Piezo1 engagement	Preclinical drug-discovery stage	[52, 256-267]
Dietary fatty acids	Not Piezo-selective	Alter membrane stiffness/fluidity and thereby modify Piezo1 mechanical sensitivity; effects vary among lipid species	In vitro Cellular; animal studies	BBB penetration and Piezo-specific effects remain uncertain	Nutritional/lifestyle intervention; no established Piezo-targeted therapy	[270, 272-277]
Physical activity and exercise	Non-selective	Shear stress/stretch→Piezo1→eNOS/NO, p38MAPK-YAP1 and other adaptive signaling	In vitro Cellular; animal studies	Excessive loading may cause Piezo1-associated cartilage injury	Clinically applicable intervention	[196, 280-283]
Ultrasound	Spatially controllable but not inherently Piezo-selective	Acoustic mechanical stimulation activates Piezo1/mechanosensitive channels and downstream Ca^{2+} signaling	In vitro Cellular; animal studies	Optimal intensity/frequency, tissue specificity and long-term safety remain undefined	Preclinical; promising non-invasive strategy	[284-286]
Delivery and modulation platforms						
Nanotechnology	Potentially high tissue/cell selectivity through targeted delivery	Enables spatially controlled Piezo activation/inhibition and targeted delivery of Yoda1, GsMTx4 or other modulators	In vitro Cellular; animal studies	Biosafety and clinical feasibility require validation	Proof-of-concept/early preclinical stage	[288-295]

5.2 Indirect mechanical and biological interventions

In addition to direct pharmacological modulation, Piezo1 activity may be influenced by indirect interventions, including natural compounds, dietary fatty acids, physical activity, and ultrasound. Although these approaches have shown potential therapeutic benefits in preclinical studies, their specificity and translational potential require further investigation.

5.2.1 Natural compounds

Traditional Chinese medicine–derived compounds, being low-toxicity and biocompatible, modulate Piezo1 to treat age-related diseases. Resveratrol reduces intra- and extracellular ROS in microglia, preserves membrane integrity and Trem2, and enhances Aβ clearance in AD models [256]. Lithospermic acid (LA) inhibits Piezo1-dependent Ca2+ influx and calcineurin/TFEB signaling to reduce ROS, mitophagy and necroptosis in

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myocardial I/R, and it alleviates CCl4-induced liver fibrosis and DKD-related renal fibrosis by suppressing Piezo1-driven inflammation and oxidative stress; these effects are blunted in macrophage-specific Piezo1 KO mice [257-259]. Paeoniflorin binds Piezo1 to block Yoda1-induced Ca2+ entry and the Piezo1/Ca2+/HIF-1α axis, restoring endothelial integrity and reducing renal fibrosis [260]. Salvianolic acid B (SalB) inhibits Yoda1- and mechanically activated Piezo1 currents, limiting Ca2+ influx, endothelial responses and foam cell formation and reducing atherosclerotic plaques, though some anti-atherosclerotic effects appear Piezo1-independent; SalB can also upregulate Piezo1 to improve post-infarction cardiac function [261, 262]. Artemisinin is a novel Piezo1 inhibitor that blocks Ca2+/PI3K-AKT signaling and alleviates Yoda1-exacerbated OA [52]. Kaempferol and quercetin inhibit Piezo1-mediated Ca2+ influx to reduce foam cell formation, oxidative stress and inflammatory NF-κB/NLRP3 signaling, with kaempferol's benefits diminished in macrophage-specific Piezo1 KO models [263, 264]. Hydroxy-safflor yellow A binds Piezo1 (docking) and suppresses the Piezo1-YAP/JNK pathway to reduce inflammation and lipid deposition in AS models [265]. The Ginsenoside Rg1-Notoginsenoside R1-Protocatechuic aldehyde combo (RRP) and Panax notoginseng saponins (PNS) improve endothelial function and limit low-shear–induced inflammation/thrombosis via Piezo1-dependent pathways (FAK-PI3K/Akt, YAP suppression), effects lost with Piezo1 silencing [266, 267]. In summary, animal and in vitro studies suggest that natural compounds may have potential value in managing age-related diseases by modulating Piezo1 activity (Fig. 3; Table 2).

5.2.2 Dietary fatty acids

Dietary fatty acids can also serve as a therapeutic intervention. The type of lipids consumed can alter membrane stiffness, which directly affects mechanosensitive ion channels [268]. Saturated fatty acids pack tightly together, thereby increasing the rigidity of the cell membrane. Consequently, greater mechanical force is required to induce a conformational shift in Piezo1 from its closed conformation to its open conformation [269]. This also explains why Piezo1 expression is upregulated in rodents fed a high-saturated-fat diet—as a compensatory mechanism in response to reduced membrane fluidity [270]. An important source of neurotransmitters in the CNS is the fatty acids that form the basic structure of cell membranes [271]. Changes in the composition of the lipid bilayer can significantly affect membrane mechanical properties, thereby altering the activity and function of Piezo1 [272]. These lipids regulate microglial Piezo1–dependent immunomodulation but normally cross the BBB poorly (requiring transport such as esterification) [273]; BBB breakdown in AD increases their brain access [274]. Diet and exercise affect metabolism and Piezo1: a high-fat diet raises Piezo1 expression and promotes metabolic syndrome and chronic inflammation—risk factors for neurodegeneration [270]. Reducing saturated fats may lower the mechanical threshold for microglial Piezo1 activation and help clear misfolded proteins, while polyunsaturated fatty acid (PUFA)-containing phospholipids enhance mechanosensitivity and could boost microglial clearance [275]. Different PUFAs have distinct effects: omega-3s lessen chondrocyte sensitivity to mechanical/Piezo1/TRPV4 activation and attenuate OA, whereas omega-6 linoleic acid increases lipid droplets and membrane fragility [276]; eicosapentaenoic acid (an omega-3) inhibits Piezo1, reducing intracellular Ca2+, apoptosis and ROS [277]. These findings indicate that dietary lipids can regulate Piezo1 through membrane mechanics and lipid-dependent signaling (Fig. 3; Table 2).

5.2.3 Physical activity and exercise

Physical activity and exercise slow age-related decline [278]. Physical activity is any skeletal-muscle movement that increases energy expenditure, while exercise is structured, repeatable activity [279]. Physical activity enhances Piezo1 activity, which is widely expressed, and increased blood flow during exercise activates endothelial and BBB-associated immune-cell Piezo1 [196]. Exercise also reduces microglia/astrocyte-mediated synaptic loss, limits OPC senescence and perivascular clustering near amyloid plaques, lowers neuroinflammation and promotes Aβ clearance [280]. These data suggest exercise may mitigate protein-aggregate neuroinflammatory diseases partly via Piezo1 regulation. Endothelial Piezo1 senses shear stress: it activates eNOS to release NO and dilate microvessels—enhancing perfusion [281]—but also generates persistent cation currents that depolarize the membrane, activate smooth-muscle VGCCs and induce vasoconstriction to raise blood pressure during exercise; endothelial Piezo1 knockout mice show impaired performance and weight loss after sustained activity [196]. In MI models, exercise upregulates cardiomyocyte Piezo1 and SERCA2, reduces apoptosis and fibrosis, and improves function via stretch-activated Piezo1→p38MAPK-YAP1 signaling and induction of FSTL1/GDF5; cardiomyocyte-specific Piezo1 knockdown abolishes these benefits [282]. These findings suggest that exercise-induced Piezo1 signaling may contribute to vascular and cardiac adaptation in experimental models.

However, the effects of exercise on Piezo1 are context-dependent and may also be detrimental. Increased

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Piezo1 expression after treadmill exercise has been associated with cartilage damage and reduced surface smoothness in mice. Excessive mechanical stress may impair chondrocyte ECM synthesis by inhibiting mitochondrial autophagy, increasing mitochondrial dysfunction, and inducing pro-apoptotic proteins and pro-inflammatory cytokines [283]. Thus, exercise-induced Piezo1 activation may exert tissue- and context-dependent effects, and its therapeutic relevance requires further investigation (Fig. 3; Table 2).

5.2.4 Ultrasound

Mechanical forces such as ultrasound activate Piezo1 and other mechanosensitive channels [284]. Transcranial 40 Hz ultrasound restores microglial Aβ clearance and reduces plaques in 5×FAD AD mice, likely by inducing an open Piezo1 conformation [284]. Low-intensity pulsed ultrasound improves bone quality and hyperglycemia in type 1 diabetic mice via Piezo1-dependent mechanotransduction, with effects comparable to insulin [285]. Higher-intensity ultrasound accelerates endochondral ossification and fracture healing in osteoporotic mice through Piezo1 (effects reduced by GsMTx4) [286]. These findings remain limited to preclinical models, and the optimal ultrasound parameters, tissue specificity, and long-term safety require further investigation (Fig. 3; Table 2).

5.3 Delivery and modulation platforms

Nanotechnology—with high drug loading, precise targeting, controllable sustained release, and the ability to cross physiological barriers—offers a promising platform for treating these conditions [287]. Nanotechnology provides a platform for spatiotemporally controlled Piezo modulation, with evidence currently derived mainly from cellular and animal studies. In neurodegenerative and cerebrovascular diseases, nanobubbles or magnetic nanostructures enable targeted mechanical stimulation or delivery to modulate neuronal or microglial Piezo1, thereby promoting Aβ clearance, neuronal differentiation, or reducing neuroinflammation [288-291]. In cardiovascular and bone repair, piezoelectric or triboelectric nanomaterials convert mechanical deformation into electrical cues to activate Piezo1–Ca^{2+} signaling, enhancing myocardial repair, osteogenesis, and angiogenesis [292-294]. Nanostructured implants can likewise regulate fibroblast responses through Piezo1/TGF-β1 signaling, highlighting the potential of surface mechanics for tissue integration [295]. Collectively, these findings support nanotechnology as a promising approach for localized Piezo regulation and tissue repair in experimental models. However, most studies remain proof-of-concept, and nanoparticle biodistribution, tissue penetration, long-term biocompatibility, manufacturing consistency, and precise control of Piezo activation remain major translational barriers (Fig. 3; Table 2).

5.4 Challenges in Piezo-targeted therapeutics

Despite their therapeutic potential, several challenges remain in developing Piezo channel-targeted drugs. First, target selectivity remains a major concern. Although Yoda1 and Jedi1/2 are widely used Piezo1 agonists, their limited selectivity may cause off-target effects. For Piezo2, the lack of well-validated, highly selective agonists and antagonists further complicates mechanistic studies and limits the development of Piezo2-targeted therapies [49]. Second, the widespread expression and diverse physiological functions of Piezo channels create challenges for tissue specificity and safety. Systemic modulation may interfere with normal mechano-transduction and cause adverse effects in healthy tissues, highlighting the need for tissue- or cell-selective targeting. Third, Piezo-mediated effects are highly context-dependent and may vary with channel subtype, cell type, and the magnitude and duration of mechanical stimulation, making optimal modulation difficult to define. Finally, pharmacokinetic, pharmacodynamic, and long-term safety data for Piezo-targeting compounds remain limited, hindering their translation from experimental tools to clinically applicable therapeutics. Addressing these challenges will be essential for the safe and effective clinical targeting of Piezo channels (Table 2).

6. Summary and perspectives

The accelerating global population aging has rendered age-related diseases—including neurodegenerative disorders, musculoskeletal degenerative diseases, cardiovascular and cerebrovascular diseases, organ fibrosis, diabetes, and hypertension—a core public health challenge worldwide. Although increasing evidence supports the involvement of both Piezo1 and Piezo2 in aging and age-related diseases, the current literature remains considerably richer for Piezo1, particularly in studies addressing tissue remodeling, inflammation, fibrosis, vascular dysfunction, and cellular senescence. Consequently, the present narrative review places greater emphasis on Piezo1, reflecting the relative depth of available mechanistic evidence rather than an assumption that Piezo1 is universally more important than Piezo2. Piezo-targeted therapies are still largely preclinical. Despite promising effects of pharmacological and non-pharmacological approaches, their specificity, safety,

efficacy, and clinical translation remain to be determined. Overall, the discovery of the mechanically activated Piezo ion channel family offers a novel perspective for elucidating the shared pathological mechanisms underlying aging and age-related disorders, and for developing intervention strategies (Fig. 4).

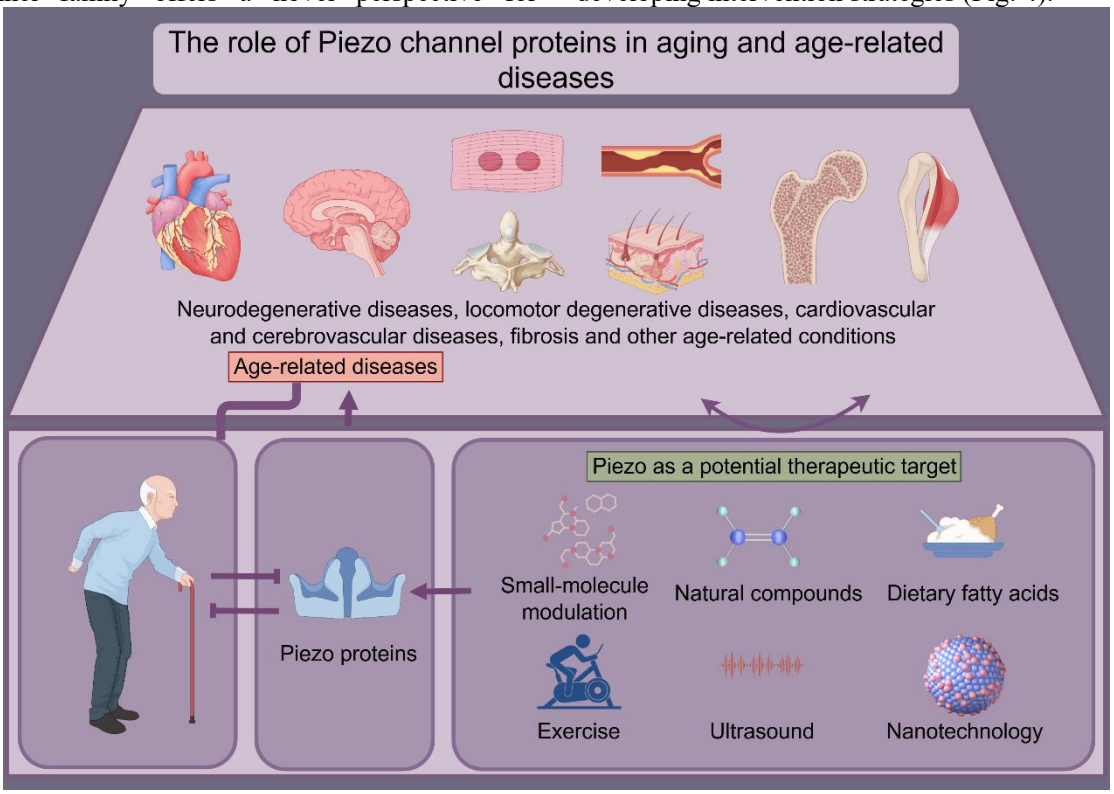


Figure 4. Piezo channels in aging and age-related diseases: mechanisms and therapeutic perspectives. Piezo-mediated mechanotransduction links age-associated mechanical alterations to multiple age-related diseases. Preclinical evidence suggests that modulating Piezo channel activity through small molecules, natural compounds, lifestyle interventions, mechanical stimulation, and delivery platforms may represent a potential strategy for regulating disease-associated cellular responses.

6.1 Comparative roles of Piezo1 and Piezo2 in age-related diseases

Although Piezo1 and Piezo2 share highly conserved structural features and both function as mechanically activated, Ca^{2+}-permeable cation channels, their physiological distributions and mechanical functions are not identical. Piezo1 is widely expressed in non-neuronal cells, including endothelial cells, fibroblasts, chondrocytes, osteocytes, and vascular cells, whereas Piezo2 is predominantly expressed in sensory neurons and specialized mechanosensory cells [19]. Both channels convert mechanical stimuli into Ca^{2+} signals, but their major mechanical sensing contexts differ [38, 39]. Piezo1 is directly activated by membrane stretch and is associated with mechanical cues including membrane tension, ECM stiffening, and fluid shear stress. In particular, the present manuscript highlights Piezo1-mediated responses to ECM stiffening in age-related tissues and to disturbed or OSS in vascular disease. By contrast, Piezo2 is more prominently associated with mechanosensory processes, including touch, pain, proprioception, and baroreception, although its expression and function in fibroblasts and other non-neuronal cells have also been reported. The available evidence does not establish universal numerical thresholds for matrix stiffness or shear stress for either channel, and their mechanical responses are likely to depend on the cellular and tissue context.

Both channels mediate Ca^{2+} influx, but their downstream effects vary according to cell type and signaling context. Piezo1 is linked to multiple Ca^{2+}-dependent pathways, including MAPK/ERK, NF-κB, NLRP3, AKT/mTOR, CaMKII, YAP/TAZ, and Wnt-related signaling, which collectively regulate inflammation, metabolism, mitochondrial homeostasis, proliferation, and ECM remodeling. Piezo2 is more closely associated with mechanosensory and neuroimmune signaling, particularly in the regulation of nociception and sensory function, while its activation in non-neuronal cells has also been implicated in fibroblast activation, tissue remodeling, and cellular stress. Thus, although Piezo1 and Piezo2 share a common capacity for

mechanically induced Ca^{2+} signaling, their downstream effects are strongly shaped by their cellular and pathological context.

These differences are particularly relevant to age-related pathology. Piezo1 is broadly implicated in pathological responses to altered tissue mechanics across vascular, musculoskeletal, cardiac, neural, and fibrotic tissues. Age-associated mechanical alterations, including ECM stiffening, disturbed fluid shear, and excessive tissue loading, are associated with Piezo1 activation and downstream responses involving inflammation, mitochondrial dysfunction, cellular senescence, fibrosis, and tissue remodeling. Piezo2, in contrast, contributes prominently to age-related changes in mechanosensation and pain, while emerging evidence summarized in this manuscript also implicates Piezo2 in pathological responses involving chondrocytes, cardiac fibroblasts, pulmonary profibrotic fibroblasts, and renal mesenchymal cells. Importantly, the functions of Piezo1 and Piezo2 are not completely redundant. In some disease settings, their effects may overlap, whereas they may also contribute to distinct pathological processes. In OA, for example, Piezo1 exhibits both protective and pathogenic roles: Piezo1 cKO delayed pain onset but ultimately exacerbated cartilage degradation and synovitis, whereas Piezo2 cKO reduced pain and preserved activity but did not protect against cartilage degeneration. Notably, combined Piezo1/2 cKO provided the greatest protection against cartilage degeneration, synovitis, and pain, highlighting the complementary contributions of the two channels to different components of OA pathology [115]. These findings suggest that targeting one channel alone may not fully address the distinct pathological processes mediated by the other. Conversely, because Piezo1 and Piezo2 also participate in physiological mechanotransduction and tissue homeostasis, including vascular regulation, cardiac function, bone integrity, baroreception, and cutaneous mechanosensation, simultaneous inhibition of both channels should not be considered universally beneficial. Therefore, Piezo1 and Piezo2 should be considered complementary but non-equivalent regulators of age-related pathology, and therapeutic modulation should be determined by disease-, tissue-, and cell-specific pathological roles rather than by simple assumptions of channel redundancy.

6.2 Potential determinants of the context-dependent effects of Piezo channels

The context-dependent effects of Piezo1 and Piezo2 may depend on cell identity, mechanical stimulation, channel subtype, and downstream Ca^{2+} signaling. Cell type influences the responses to Piezo activation because the associated signaling networks and physiological functions differ among endothelial cells, immune cells, neurons, and chondrocytes. Consequently, Piezo activation may support tissue homeostasis in some contexts but promote inflammation or tissue damage in others. Mechanical stimuli also vary in type, magnitude, frequency, and duration. While physiological loading may maintain tissue homeostasis, excessive or sustained stimulation may trigger maladaptive responses. In addition, Piezo1 and Piezo2 have distinct expression patterns and functional roles, suggesting that their effects should be considered in a subtype- and tissue-specific manner. The amplitude, duration, and spatiotemporal patterns of Ca^{2+} signals may further shape downstream responses, including MAPK/ERK- and NF-κB-associated inflammation, metabolic changes, mitochondrial dysfunction, cellular senescence, and tissue remodeling. These factors may interact, and their relative contributions may vary across tissues, experimental models, and disease stages. However, the mechanisms underlying these context-dependent effects require further investigation.

6.3 Open questions and future directions

Despite remarkable progress in Piezo channel research on age-related diseases, several critical scientific questions and translational challenges remain unresolved. First, the tissue- and cell-specific functions of Piezo1 and Piezo2, their potential compensatory effects, and changes in channel activity during aging remain incompletely understood. Direct comparisons between the two subtypes, combined with subtype-selective genetic perturbation and appropriate rescue experiments, would help define their respective roles in tissue aging and age-related pathologies. Second, most existing Piezo modulators are non-selective compounds; the development of tissue-specific agonists or inhibitors lags behind, and their long-term safety and efficacy await clinical validation. Third, the crosstalk mechanisms between Piezo channels and core hallmarks of aging (e.g., telomere attrition, epigenetic alterations) remain unclear, and the synergistic interactions between mechanical signals and metabolic, immune, and neural regulatory networks require systematic exploration. Fourth, the clinical translational value of Piezo channel-based biomarkers (e.g., erythrocyte Piezo1 expression, urinary Piezo1 expression) needs to be validated in large-scale cohorts.

In conclusion, Piezo channels, as key molecular hubs linking the mechanical microenvironment to aging pathologies, serve not only as critical targets for elucidating aging mechanisms but also as novel directions for developing anti-aging disease-modifying therapies. Future research should focus on tissue-specific regulatory mechanisms of Piezo channels, develop highly selective

and low-toxicity targeted drugs, integrate multi-modal intervention strategies including pharmacology, exercise, physical stimulation, and nanodelivery, and drive the translation of basic research findings into clinical applications. These efforts will ultimately provide a novel theoretical foundation and therapeutic paradigm for achieving healthy aging and systematically combating age-related diseases.

CRediT authorship contribution statement

Yan Li: Writing–review & editing, Writing–original draft, Conceptualization. Jing-jing Wang: Writing–review & editing. Tian-tian Xue: Writing–review & editing. Yan-bin Li: Writing–review & editing. Guo-qing Zheng: Writing–review & editing, Conceptualization.

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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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