Roles of Piezo1 in chronic inflammatory diseases and prospects for drug treatment (Review)

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Abstract. The human body is chronically stimulated by various mechanical forces and the body cells can sense harmful stimuli through mechanotransduction to induce chronic inflammation. Piezo type mechanosensitive ion channel component 1 (Piezo1), a novel transmembrane mechanosensitive cation channel, is widely expressed in inflammatory cells, such as neutrophils, macrophages and endothelial cells, as well as in non-inflammatory cells, such as osteoblasts, osteoclasts and periodontal cells. A growing number of studies have demonstrated that Piezo1 senses changes in environmental mechanical forces, regulates cellular functions and influences the development and regression of chronic inflammation. The present study summarized the roles of Piezo1 and its possible mechanisms in some common chronic inflammatory diseases and evaluated the potential application of drugs that modulate its activity, so as to prove that Piezo1 is likely to become a new target for the treatment of inflammatory diseases.

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1. Introduction

Most physiological processes are associated with mechanical forces and cells can sense whether the mechanical forces of the microenvironment have changed and can make proper adaptation in response to the changes. Mechanotransduction is mediated by a wide variety of mechanosensitive channel proteins found in cells. Piezo type mechanosensitive ion channel component 1 (Piezo1) is a novel mechanosensitive cation channel discovered by Coste *et al* (1) in a mouse neuroblastoma cell line in 2010. The human Piezo1 gene, Fam38a, is located in chromosome 16q24.3 and contains 51 exons and 2,520 amino acids (1). Piezo1 is a transmembrane protein and the Piezo protein family has a unique sequence that lacks sequence homology with any other known cation channel protein families (2).

As a part of the cellular response to mechanical forces, Piezo1 senses mechanical stress and triggers inflammation (3). In contrast to Transient Receptor Potential Vanilloid 4 (TRPV 4), which is activated in response to mechanical loads at physiological levels, Piezo1 is activated in response to supraphysiological mechanical deformation (>50% cell deformation) and acts directly by physically deforming and opening channels through increased cell membrane tension (4,5). In addition, Piezo1 is able to respond to a variety of mechanical stimuli and convert mechanical stimuli into intracellular signaling cascades in multiple systems, such as the circulatory and respiratory systems, which influence the development of chronic inflammatory diseases (6). For example, both TRPV4 and Piezo1 are involved in mediating deflection-gated currents in chondrocytes, but TRPV4 cannot be effectively gated by pressure-induced membrane stretch and only Piezo1 mediates stretch-activated currents (7). This suggests that Piezo1 plays a more extensive role in the mechanotransduction of inflammatory responses. The present study analysed how Piezo1 conducts mechanical stimuli to modulate inflammatory responses in osteoarthritis, atherosclerosis, pulmonary inflammation, periodontitis and Alzheimer's disease and summarizes agonists and antagonists that modulate Piezo1 activity and give a further exploration of their potentials for clinical treatment.

2. Basic structure and function of Piezo1

Using cryo-electron microscopy, researchers have found that the structure of the Piezo1 protein is a three-bladed propeller-like

trimer consisting of a unique central pore domain and three peripheral blade-like propellers (8) (Fig. 1A). Piezo1 is encapsulated in the lipid bilayer, where the three propeller-like structural domains extend outward in the lipid bilayer. Each blade-like propeller contains a unique 38 transmembrane α-helices, which can be divided into three parts based on their structural and functional characteristics: the N-terminal blade in the mechanosensory module, the C-terminal ion-conducting pore module and the transactivation module consisting of the anchor and the beam (9). Specifically speaking, the N-terminal contains nine repetitive folded structures with four α-helices (transmembrane α-helices 1-36) called transmembrane helical units (THUs), which serve as the backbone of each blade (8). The remaining two α-helices (37 and 38) at the C-terminal, referred to as the inner helix (IH) and outer helix (OH) (10), constitute the C-terminal intracellular structural domain (CTD) with the central pore module of Piezo1. At the top of the central pore, there exists a cap of negatively charged residues consisting of the C-terminal extracellular structural domains (CED) and deletion of the cap structure or restriction of the movement of the cap structure prevents the channel from opening, suggesting that the conformational changes of the cap structure is necessary for Piezo1 to perform its function of mechanical gating (11). The anchor domain consists of three helices (α1, α2 and α3) and serves as a bridge connecting THU9 and OH-IH (12). The beam is located on the inner surface of the cell and connects THU7 and THU8 to the center pore domain, supporting the blade-like propeller (9). The beam structure contains a convoluted helical motif LAQLKRQM (1341-1348) near the CTD, in which mutating L1342 and L1345 decreases the mechanosensitivity of Piezo1 and markedly reduces poking-induced currents, suggesting that L1342 and L1345 are important for the mechanical activation of Piezo1 (9). Further studies have reveals that L1342 and L1345 acts as fulcrums to form a lever-like structure that effectively amplifies distant mechanical stimuli and ensures selective cation penetration (13) (Fig. 1B).

Piezo1 is mainly located on plasma membranes such as endoplasmic reticulum, cytoplasmic compartment and nuclear envelope near the nucleus (9). The existence of Piezo1 enables cells to sense such mechanical forces as radial force, membrane stretch, compression, shear stress, matrix stiffness and osmotic pressure. When these mechanical forces act on the cell membrane, Piezo1 is induced to shift from the closed state to the open state, allowing the passage of cations such as Ca^{2+}, K^+ and Na^+ and regulating cellular physiological activities such as protein synthesis, secretion and cell migration, differentiation, proliferation and apoptosis (5) (Fig. 1C). When cells are subjected to non-physiological mechanical stimuli that damage tissues and induce inflammation, the progression of inflammation is often accompanied by alterations in the mechanical forces of the microenvironment. Piezo1, as a mechanosensitive channel, plays an important role in the onset, development and prognosis of inflammation. For example, in aortic stenosis, monocytes sense shear stress and activate via Piezo1, adhering to endothelial cells and leading to valve inflammation (14). Piezo1 on macrophages is stimulated by cyclic hydrostatic pressure (CHP) to promote expression of inflammatory factors and macrophage M1-type polarization, exacerbating the inflammatory response in the lungs (15). In addition, inflammatory responses around bone tissue are often accompanied by alterations in osteoblast activity, leading to pathological changes in bone and its surrounding structures. Piezo1 mediates mechanical load in osteoblasts and coordinates osteoblast-osteoclast crosstalk in bone to maintain bone mass *in vivo* (16). In osteoarthritis, Piezo1 induces the chondrocyte apoptosis and the release of inflammatory factors that destroy articular cartilage (17). In chronic inflammation, Piezo1 senses changes in microenvironmental homeostasis and regulates cellular function and its dysfunction tends to accelerate the development of chronic inflammation (Fig. 2).

3. Association of Piezo1 with chronic inflammatory diseases

Osteoarthritis (OA). OA is a common degenerative disease of the joints. In addition to destroying articular cartilage, OA is now more widely recognized as a lesion of the entire joint. Inflammatory exudation leads to increased intra-articular mesenchymal fluid and increased pressure in the joint cavity, initiating apoptosis and the inflammatory program (18). A study has shown that Piezo1 is expressed in chondrocytes, osteoblasts and osteoclasts and regulates the onset and progression of OA by mediating mechano-biological signaling (19).

Mechanical stress at physiologic level is the basis for the normal functioning of bones and joints and excessive mechanical loading of bones causes inflammation and degeneration. The ionic homeostasis of internal environment is the basis for chondrocytes to exercise normal functions. In OA, the expression of Piezo1 in chondrocytes is upregulated under supraphysiological levels of mechanical stimulation and Ca^{2+} signaling is continuously enhanced, which ultimately leads to apoptosis (20). Another study notes that excessive apoptosis in chondrocytes under excessive mechanical stress stimulation is mediated by Piezo1-mediated downstream signaling molecules MAPK/ERK5 and MAPK/ERK1/2: This process produces a large number of oxygen radicals and inflammatory mediators (for example, IL-1b and TNF-α), which damage the new chondrogenic tissues and blood vessels and further aggravate the apoptotic death of chondrocytes, thus forming a vicious cycle (17). The use of the Piezo1 inhibitor GsMTx4 delays the progression of osteoarthritis (17). The microRNA (miR)-155-5p is an mRNA associated with cell proliferation, differentiation and inflammatory responses. Activation of Piezo1 also leads to the upregulation of miR-155-5p, which brings about the downregulation of the downstream target gene GDF6 and accelerates chondrocyte senescence and cartilage degradation and induces inflammatory responses to disrupt bone and joint homeostasis (21). Reintroducing GDF6 into overloaded chondrocytes reverses the negative effects of inflammation, such as collagen loss and impaired chondrocyte proliferation (21).

Piezo1 is also involved in regulating the cellular activities of osteoblasts and osteoclasts and modulating the development of OA (22). In osteoblasts, Piezo1 senses mechanical loads, which is important for cell proliferation, migration, differentiation and bone formation. An *in vitro* study has shown that under shear stress stimulation, expression of Piezo1 increases, activating the AKT/GSK-3β/β-catenin signaling pathway and promoting the expression of the osteoblast gene Runx2 (23). The knockout of Piezo1 in osteoblast lineage cells

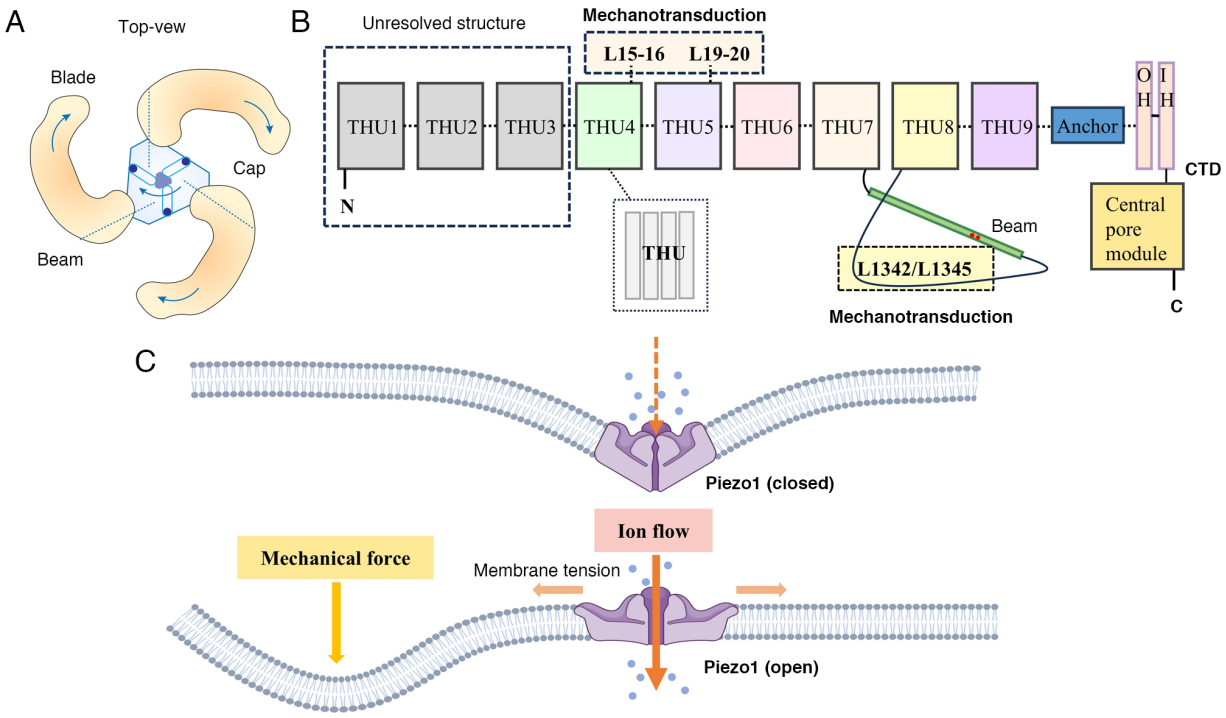

Figure 1. The structure of Piezo1. (A) The top view of the three propeller-like structural domains of Piezo1. (B) Each blade-like propeller of Piezo1 contains a unique 38 transmembrane α-helices: The N-terminal blade in the mechanosensory module, the C-terminal ion-conducting pore module and the transactivation module consisting of the anchor and the beam. L1342 and L1345 acts as fulcrums to form a lever-like structure that ensures selective cation penetration. (C) Mechanism of the activation of Piezo1 by extracellular mechanical forces. Piezo1, Piezo type mechanosensitive ion channel component 1; THUs, transmembrane helical units; IH, inner helix; OH, outer helix; CTD, C-terminal intracellular structural domain; CED, C-terminal extracellular structural domains.

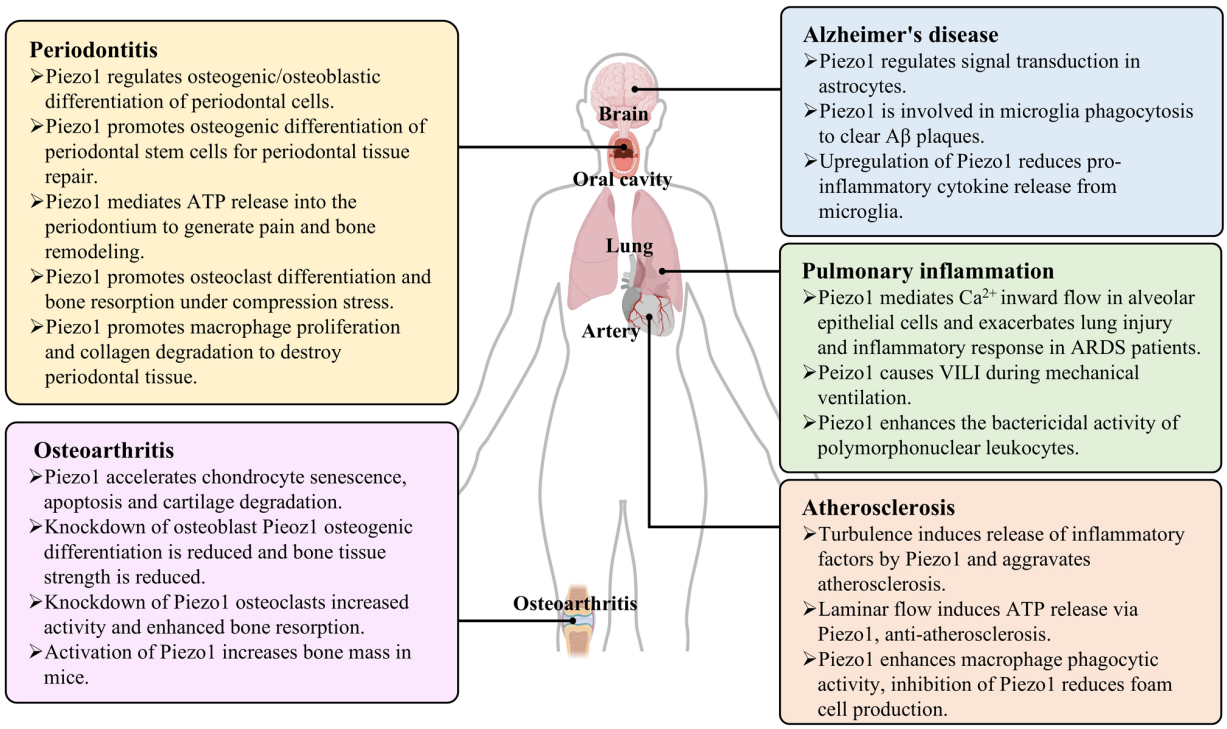

Figure 2. Role of Piezo1 in chronic inflammatory diseases. Piezo1, Piezo type mechanosensitive ion channel component 1; VILI, ventilator-associated lung injury; ARDS, acute respiratory distress syndrome.

impairs osteogenesis, resulting in structural disruption and reduced strength of bone (23). Meanwhile, Piezo1-deficient osteoblastic cells are also able to increase the number and activity of osteoblasts by regulating the Yes-associated protein (YAP)-dependent expression of type II and type IX collagen, which enhances bone resorption, leading to further bone loss

and spontaneous fractures (24). The use of the Piezo1 agonist Yoda1 increases *in vivo* bone mass and expression of bone formation markers in mice (25). Notably, in the absence of long-term mechanical loading, bone mass and bone strength also rapidly decrease. Piezo1-deficient mice are resistant to bone loss and resorption caused by lack of mechanical loading (26).

These findings reveal the role of Piezo1 in chondrocyte apoptosis and osteoblast-osteoclast crosstalk, providing a potential therapeutic target for OA.

Atherosclerosis. Atherosclerosis (AS) is an inflammatory disease caused by multiple factors such as obesity, hypertension, diabetes and hyperlipidemia, and vascular endothelial cell injury is the initiating factor of AS (27). Subsequently, cholesterol and lipids in the blood are deposited under the endothelial cells, attracting monocytes to aggregate and then differentiate into macrophages, which phagocytose lipids to convert into foam cells and secrete pro-inflammatory factors, leading to inflammatory reactions (28). During this process, vascular endothelial cells are continuously subjected to shear stress from blood flow. A study has shown that the expression of Piezo1 increases markedly in carotid plaque tissues of AS mice and is involved in several response processes in AS, such as vascular endothelial cell injury and macrophage activation (29).

It has been found that Piezo1 is abundantly expressed in vascular endothelial cells and has both injurious and anti-injurious effects, depending on the type of blood flow signaling to which the vascular endothelial cells are subjected (30). Blood flow is categorized into laminar and turbulent flow, with laminar flow leading to nitric oxide (NO) formation and the endothelial barrier acting as a protective shield against inflammation and turbulent flow leading to vasoconstriction, endothelial barrier disruption and atherosclerosis development (31). Cells in turbulence are subjected to forces in random directions that activate Piezo1, which induces inflammatory signaling through integrin-associated PECAM-1/VE-calmodulin/VEGFR2 and PI3K-dependent activation, further leading to FAK-dependent nuclear factor κB (NF-κB) activation (32). The activation of NF-κB promotes the leukocyte adhesion molecule VCAM-1, ICAM-1 and chemokine CCL2 expression, thus promoting AS development (33). By contrast, vascular endothelial cells in continuous laminar flow are subjected to shear forces only in the direction of the cytosolic long-axis, which induces the release of ATP via Piezo1 and activates P2Y purinoceptor 2 ($P2Y_2$) receptors and Gq/G11-mediated signaling. This in turn leads to the phosphorylation of protein kinase B (AKT) and release endothelial nitric oxide synthase (eNOS), thus demonstrating the anti-atherosclerotic process (32,34). Meanwhile, a certain concentration of oxidized low-density lipoprotein (ox-LDL) induces the expression of Piezo1 in endothelial cells, activates YAP and transcriptional coactivator with PDZ-binding motif (TAZ) and enhances JNK signaling pathway to promote inflammation and AS progression (35). The pharmacological inhibition of Piezo1 or the knockdown of the Piezo1 gene effectively reduces atherosclerotic plaque formation and attenuates the atherosclerotic inflammatory response in vascular endothelial cells (30).

Piezo1 has also been confirmed to be highly expressed in monocytes (36). Atherosclerotic plaques lead to arterial stenosis and increased shear stress of blood flow, which promotes the activation of a series of monocytes through Piezo1 and enhances macrophage phagocytic activity, ox-LDL uptake and cytokine expression of monocytes (37). The knockdown of Piezo1 gene is able to reduce atherosclerotic plaque formation (38). Transcatheter aortic valve implantation (TAVI) is an effective treatment for aortic stenosis. As the mechanism of the role of Piezo1 in the development of AS is becoming clearer, researchers have found that TAVI reduces Piezo1-mediated activation of monocyte and exerts an anti-inflammatory effect (14). In addition, Kaempferol inhibits foam cell formation and ameliorates AS by inhibiting Piezo1 channels on macrophages and Ca^{2+} endocytosis to regulate MAPK/NF-κB and NFE2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) downstream signaling (39).

In conclusion, Piezo1 promotes inflammatory responses in vascular endothelial cells and monocyte activation in AS and inhibition of Piezo1 can delay the progression of AS. Piezo1 has promising treatment prospects in AS researches.

Pulmonary inflammation and lung injury. Mechanical stress plays a crucial role in the development, functional maturation and pathogenesis of lung tissue. For example, alveolar epithelial cells are predominantly exposed to mechanical stress during respiration and vascular endothelial cells are mainly exposed to shear stress, strain and hydrostatic pressure, both of which play an important role in the perception of mechanical stress in lung tissue (40). It has been shown that Piezo1 is highly expressed in alveolar epithelial cells, endothelial cells and monocyte macrophages in response to lung mechanical stress and that it participates in pulmonary inflammation through multiple mechanisms (41).

Piezo1 is one of the major ion channels mediating Ca^{2+} endocytosis in alveolar epithelial cells. In acute respiratory distress syndrome (ARDS), mechanical stress induces the activation of Piezo1, which mediates apoptosis of type II alveolar cells through the Bcl-2 pathway and induces abnormal secretion of alveolar surface-active substances, thereby exacerbating lung injury and inflammation in ARDS patients. The inhibition of Piezo1 attenuates these responses (42). Piezo1 in human pulmonary microvascular endothelial cells participates in the mechanism of ventilator-associated lung injury (VILI) and cyclic stretch induces cell apoptosis in mechanical ventilation therapy for ARDS by activating the RhoA/ROCK1 signaling pathway (43). Blockade of Piezo1 reduces the concentrations of TNF-α, IL-1β and IL-6 and attenuates the inflammatory response in lung tissues of rats with VILI (43). In addition, Piezo1 can induce the detachment of AREG protein from the cell surface, which upregulates metalloproteinase ADAM10 and ADAM17 activity, further breaking down intercellular junction proteins and causing secondary damage to the lung endothelial barrier and VILI (44).

Piezo1 responds to CHP in the lungs, mediating inflammatory responses in lung immune cells. The sensing of CHP through Piezo1 in lung monocytes promotes the activation Ca^{2+}-activating protein-1 (AP-1) and transcription of endothelin-1 (EDN1), leading to the stabilization of HIF1α, which triggers the pro-inflammatory state during pulmonary

Table I. Research on Piezo1 in chronic inflammatory diseases.

First author/s, year	Disease	Factors activating Piezo1	Animals/cells/tissues	Possible mechanisms	Negative regulation of Piezo1	Results	(Refs.)
Li *et al*, 2016	OA	Compressive stress	Chondrocytes	Activates MAPK/ERK1/2 signaling pathway, upregulates apoptosis related genes Bcl-2, Bax, and caspase-3 in the nucleus	GsMTx4	Reduces apoptosis of chondrocytes	(17)
Qin *et al*, 2024	OA	Compressive stress	Mice/chondrocytes/ joint cartilage	Piezo1/miR-155-5p/GDF6/ SMAD2/3 axis, upregulates miR-155-5p and downregulates GDF6	Dooku1	Decreases miR-155-5p expression, ameliorated OA deterioration	(21)
Albarrán-Juárez *et al*, 2018	AS	Oscillatory flow	Mice/human umbilical artery endothelial cells	G_q/G_{11}-mediated PECAM-1/ VE-calmodulin/VEGFR2 and PI3-kinase-dependent activation, activate FAK-dependent NF-κB pathway	siRNA-mediated knockdown	Reduces inflammation and AS progression	(32)
Pourteymour *et al*, 2024	AS	Yoda1	Mice/monocyte differentiated macrophages	Mitochondrial DRP1 phosphorylation, mtROS production, mitochondrial fragmentation	siRNA-mediated knockdown	Reduces the expression of anti-inflammatory and anti-apoptotic molecules	(37)
Huang *et al*, 2021	VILI	Cyclic stretch	Rats/human pulmonary microvascular endothelial cells	Activates RhoA/ROCK pathway	GsMTx4, siRNA-mediated knockdown	Alleviates the inflammatory reaction of lung tissue	(43)
Solis *et al*, 2019	Bacterial pneumonia	CHP	Mice/monocytes	Activates AP-1, stabilizes HIF1, secrets EDN1 and CXCL2	Knockout	Reduces pulmonary inflammation	(45)
Mukhopadhyay *et al*, 2024	Bacterial pneumonia	Tension	Mice/ polymorphonuclear leukocytes	HIF1α-dependent expression of the NADPH oxidase isoform NOX4 gene	Knockout	Severe infection	(46)
Hurrell *et al*, 2024	Allergic asthma	Yoda1	Mice/group 2 innate lymphoid cells	KLF2-mediated inhibition of NF-κB signaling and ILC2 cytokine secretion	Knockout	Severe infection	(47)
Jiang *et al*, 2024	Periodontitis	Compressive force	Rats/PDLCs	Increases the RANKL/OPG ratio; activates Wnt/β-catenin signaling pathway	GsMTx4, siRNA-mediated knockdown	Reduces bone resorption and osteogenesis	(50)

Table I. Continued.

First author/s, year	Disease	Factors activating Piezo1	Animals/cells/tissues	Possible mechanisms	Negative regulation of Piezo1	Results	(Refs.)
Jin *et al*, 2015	Alveolar bone injury	Compressive force	Periodontal ligament cells (PDLCs)	nuclear translocation of NF-κB	GsMTx4	Reduces mechanical stress-induced osteoclastogenesis	(51)
Xu *et al*, 2022	Periodontitis	Mechanical tension	Mice/macrophage	Activates Piezo1-PI3K/AKT-Ccnd1 axis	GsMTx4	Reduces macrophage proliferation	(59)
Zhao *et al*, 2023	Periodontitis	LPS	Macrophage	Generates more ROS via Piezo1, causing oxidative stress and enhancing MMPs secretion	GsMTx4	Reduces pro-inflammatory cytokines	(60)
Velasco-Estevez *et al*, 2020	AD	LPS	Astrocytes	Regulates intracellular Ca^{2+} signaling	GsMTx4	Enhances cell migration	(65)
Jäntti *et al*, 2022	AD	Yoda1	Mice/microglia	Mediates Ca^{2+} influx, enhances lysosomal activity	None	None	(69)
Liu *et al*, 2021	AD	LPS	Microglia	Inhibits JNK1 and mTOR pathway	GsMTx4, siRNA-mediated knockdown	Alleviates high-glucose cytotoxicity and restores microglial immune function	(70)
Liu *et al*, 2024	AD	LPS	Mice/astrocytes/ microglia	Inhibits the transduction of NF-κB p65 signaling	ω3-PUFA	Inhibits LPS-induced activation of Piezo1 by upregulating miR-107, reduces the inflammatory activation	(71)

OA, osteoarthritis; AS, atherosclerosis; VILI, ventilator-associated lung injury; CHP, cyclic hydrostatic pressure; AD, Alzheimer's disease; LPS, lipopolysaccharide; PUFA, polyunsaturated fatty acids; DRP1, dynamin-related protein 1; AP-1, activating protein-1; HIF, hypoxia inducible factor-1; END1, endothelin-1; CXCL2, chemokine CXC ligand 2; NADPH, nicotinamide adenine dinucleotide phosphate; ILC2, group 2 innate lymphoid cells; ROS, reactive oxygen species; MMPs, matrix metalloproteinases.

infection (45). However, the activation of Piezo1 in polymorphonuclear leukocytes upregulates nicotinamide adenine dinucleotide phosphate oxidase 4 which enhances bactericidal activity and thus promotes the resolution of bacterial pneumonia (46). Moreover, in group 2 innate lymphoid cells (ILC2) in the lung, Piezo1 reduces ILC2 oxidative metabolism, thereby inhibiting ILC2 mediated type 2 inflammation (47).

Therefore, Piezo1 is expected to be a therapeutic target for lung inflammation and the use of Piezo1 modulators to regulate the function of alveolar epithelial cells and monocyte macrophages offers a possible option for the treatment of lung inflammation.

Periodontitis. Periodontitis is an inflammatory and destructive disease caused by plaque microorganisms on tooth-supporting tissues, destroying periodontal ligament, alveolar bone and dental bone and is the leading cause of tooth loss in adults. In addition to oral bacteria, excessive mechanical forces such as occlusal trauma promotes the progression of periodontitis and exacerbate alveolar bone resorption (48).

Periodontal ligament cells (PDLCs) play an important role in maintaining periodontal homeostasis and regulating periodontal tissue remodeling. PDLCs are mechanically stimulated to produce a variety of inflammatory factors including prostaglandins, leukotrienes, IL-1, IL-6 and TNF-α (49). Piezo1 plays an important role in the perception of mechanical stimuli in PDLCs. Piezo1 enhances the expression of osteogenesis-related genes RUNX2 and OSX under compressive stress and regulates PDLCs through the Wnt/β-catenin pathway (50). Piezo1 is also involved in compressive stress-induced osteoclast formation through the NF-κB signaling pathway in PDLCs (51). A further study has shown that compressive stress stimulates the expression of RANKL and decreases the expression of osteoprotegerin (OPG) in PDLCs, thereby promoting RANKL-mediated osteoclastogenesis by increasing the RANKL/OPG ratio (50). Low-intensity pulsed ultrasound is able to downregulate the expression of Piezo1 in PDLCs and reduce alveolar bone resorption under compressive stresses (52). It may be a therapeutic tool to reduce bone resorption in periodontitis.

PDLCs contain a variety of cell types, including periodontal ligament stem cells (PDLSCs) and periodontal ligament fibroblasts (PDLFs), which are also important for maintaining periodontal homeostasis. PDLSCs are capable of regenerating osteoid-like and periodontal membrane-like tissues and promoting periodontal tissue repair and have pro-periodontal regeneration potential (53). A study demonstrated by an *in vitro* mechanical tension stress cell model shows that mechanical tension stress upregulates the expression of Piezo1, activates the Notch1 signaling pathway, increases the expression of osteogenic genes and promotes the osteogenic differentiation of PDLSCs (54). PDLFs play an important role in alveolar bone remodeling by increasing the formation of osteoclast in response to inflammation-induced or mechanical force stimuli (55). *In vitro* studies have shown that PDLFs activate Piezo1 after mechanical stimulation, which mediates Ca^{2+} endocytosis and releases ATP to the periodontium (56). ATP activates multiple receptors that produce pain and bone remodeling (57).

In addition, macrophages also play a crucial role in the inflammatory response and alveolar bone resorption in periodontitis. Appropriate mechanical stimulation induces macrophage polarization toward M2 type through Piezo1-mediated p53 acetylation and deacetylation and releases TGF-β1 to promote osteogenic differentiation of bone marrow mesenchymal stem cells (58). However, under non-physiological mechanical stimulation, macrophages express high levels of Piezo1, which elicits an inflammatory response and promotes osteoclast differentiation and bone resorption. Specifically, high expression of Piezo1 increases the expression of cell cycle protein D1 (Ccnd1), a potential downstream effector of the AKT/GSK3β signaling pathway, promoting macrophage proliferation (59). In addition to this, macrophages in periodontitis tissues mediate the degradation of collagen in gingival fibroblasts by Piezo1-mediated matrix metalloproteinases (MMPs), thereby destroying periodontal tissues (60).

In brief, Piezo1 regulates osteogenic/osteoclastic differentiation of PDLCs and macrophages under mechanical stimulation and is an important mechanotransduction channel in periodontal destruction and alveolar bone resorption in periodontitis.

Alzheimer's disease (AD). AD is a progressive neurodegenerative disease in which amyloid-β (Aβ) plaques are deposited in cells of normal brain tissue leading to increased hardness of the brain matrix under the microscope and ultimately causing necrosis of nerve cells and brain tissue damage (61). Neuroglial cells are another large group of cells in the nervous system besides neurons, which are highly mechanosensitive during their growth and respond rapidly to changes in the stiffness of the surrounding environment through mechanosensitive ion channels (62).

Astrocytes, the most abundant glial cell type in the brain, exhibit a 'reactive' phenotype with increased intermediate filament expression in response to amyloid plaque deposition (63). In the brains of AD patients, glial cells are the most abundant type of glial cell in the brain and astrocytes are more reactive and release more pro-inflammatory cytokines (64). Peripheral infections and aging upregulate Piezo1 expression in reactive astrocytes and this upregulation is not detected in non-AD cells (62). Astrocytes upregulate Piezo1 channels in response to lipopolysaccharide (LPS), attempting to inhibit the release of pro-inflammatory cytokines and suppress neuroinflammation (65). Piezo1 may potentially regulate signaling in reactive astrocytes, thereby influencing astrocyte phenotype.

Microglia are phagocytic and scavenging, capable of removing dying neurons and engulfing abnormal protein or lipid plaques in neurodegenerative diseases. In AD, microglia proliferate, activate and accumulate around Aβ plaques and invade their nuclei to phagocytose and remove Aβ plaques (66). Through researchers have found that on the one hand, microglia express an innate immune receptor, TLR4, which is activated by Aβ plaques and infection-associated bacterial LPS, while upregulating Piezo1 (67). Piezo1 synergizes with TLR signaling to induce Ca^{2+} endocytosis and activate the CaMKII-Mst1/2-Rac axis that exerts phagocytic and scavenging effects (68). On the other hand, Aβ plaques may directly upregulate Piezo1 in microglia, thereby affecting

the immunoreactivity of microglia. It has been demonstrated that Piezo1 is highly expressed in the cell membrane and nucleus of microglia derived from artificially induced pluripotent stem cells. When Piezo1 is activated by the agonist Yoda1, the functional phenotype of microglia is altered and its migration, phagocytosis and lysosomal activity are enhanced, thereby assisting the clearance of Aβ plaques from the body (69). Aβ plaques stimulate microglia to release a variety of pro-inflammatory cytokines, leading to neuroinflammation, neuronal dysfunction and death. In addition to its involvement in the clearance of Ab plaques by microglia, Piezo1 is also involved in the inflammatory activation of microglia. In LPS-induced upregulation of Piezo1, Piezo1 reduces LPS induced pro-inflammatory cytokines TNF-α, IL-1β and IL-6 through the expression of JNK1 and mTOR signaling pathways (70). Polyunsaturated fatty acid ω3-PUFA upregulates miR-107 to inhibit LPS-induced Piezo1 activation and NF-κB p65 signaling pathway, providing a potential treatment for neuroinflammation (71).

In summary, Piezo1 regulates signal transduction in reactive astrocytes in the brains of AD patients, assists microglia in phagocytosis to clear Aβ plaques and reduces the release of inflammatory factors. It may hopefully become a novel drug target for the treatment of AD in the future.

4. Mechanism of Piezo1 transduction of inflammatory signaling

The concentration of free Ca^{2+} in the cytoplasm is much lower than that in the extracellular and various cellular stimuli increase the concentration of free Ca^{2+} in the cytoplasm (72). Based on the localization of Piezo1 in cells, activation of Piezo1 not only triggers the flow of extracellular Ca^{2+} to the intracellular compartment, but also promotes the release of Ca^{2+} from calcium stores, resulting in an increase in intracellular Ca^{2+} concentration (65). As a second messenger, Ca^{2+} plays direct and robust roles in a number of biological processes, as an increasing number of studies have reported over the last decades (73,74). The enhancement of Ca^{2+} signaling induces inflammatory responses and other cellular events through signaling cascades. Ca^{2+} activates downstream effector molecules (such as CaMK kinase family and transcription factor NFAT) by binding to calmodulin (73). Ca^{2+} collaborates with calcium channels (such as TRP and Piezo) and endoplasmic reticulum/mitochondrial storage systems to regulate key physiological processes, such as cell proliferation, apoptosis and immune response (74). Piezo1-mediated Ca^{2+} signaling participates in the inflammation through a variety of signaling pathways.

There are obvious differences in the role and downstream mechanisms of Piezo1 in various tissue inflammations (Table I). MAPK/ERK signaling pathway is an important intracellular signaling pathway involved in the regulation of various biological processes such as cell proliferation, differentiation, migration and apoptosis. A study has shown that Piezo1 regulates inflammatory responses by activating the MAPK/ERK signaling pathway. For instance, in chondrocytes, Piezo1 activation promotes apoptosis through the classical MAPK/ERK1/2 signaling pathway (17). Specifically, mechanical stress activates Piezo1, leading to an increase in intracellular Ca^{2+} concentration. This in turn activates ERK1/2, which ultimately causes changes in apoptosis-related genes Bcl-2, Bax and caspase-3, leading to apoptosis.

In addition, NF-κB signaling pathway is also a core regulatory pathway of inflammatory response, which is involved in the transcriptional regulation of various inflammatory factors. Research has shown that Piezo1 regulated the inflammatory response by activating the NF-κB signaling pathway. In endothelial cells, Piezo1 activation promotes inflammatory responses through the NF-κB signaling pathway (32). Specifically, mechanical stress activates Piezo1 in endothelial cells, resulting in elevated intracellular Ca^{2+} concentration, which in turn activates NF-κB and promotes the release of inflammatory factors such as TNF-α, IL-1β and IL-6. This plays an important role in the inflammation of atherosclerosis.

Apart from these two classic inflammatory pathways, signaling pathways such as inflammasome NLRP3 (75), AKT/mTOR (70) and CaMKII-Mst1/2-Rac (68) are also involved in Piezo1-mediated inflammatory response. Although the specific mechanisms and targets of action vary in different diseases, the core mechanism is to activate downstream signaling pathways by regulating intracellular Ca^{2+} concentration, thereby regulating inflammatory responses.

5. Piezo1 is a potential therapeutic target

Since Piezo1 plays an important role in a number of physiological and pathological processes, targeted modulation of Piezo1 activity may become a novel strategy for the treatment of a number of diseases. Although the specific ligand binding mechanism of Piezo1 has not been fully elucidated, there are a number of agonists and antagonists that have produced effects *in vivo* and *in vitro* (Table II).

Piezo1-specific agonists

Yoda1. Researchers screened millions of compounds and discovered Yoda1, the first synthetic small molecule agonist targeting Piezo1 (76). Structural analysis of Yoda1 revealed that the (2.6-dichlorobenzyl)thioether group and pyrazine and thiadiazol groups are important for its agonism (77). Yoda1 binds to Piezo1 and induces a conformational change in the channel that opens the channel and effectively lowers the mechanical activation threshold of Piezo1 (78). In some animal experiments, Yoda1 can activate Piezo1 to regulate palatal bone development (79), regulate lung fibroblasts to improve airflow and also increases bone mass and reduces bone loss in mice, making it a potential target for the treatment of osteoporosis (80). A recent study found that the association of Yoda1 with low-magnitude high-frequency (LMHF) vibration synergistically promotes YAP nuclear translocation and strengthens osteoblast responses to mechanical stimuli, potentially enhancing the efficacy of LMHF vibration in the treatment of osteoporosis (81). However, this finding needs to be further validated in animal models and clinical trials *in vivo*. Apart from the shortcomings of the experimental model, Yoda1's poor solubility and certain cytotoxicity have hampered further clinical research (77).

Jedi1/2. Through high-throughput screening, researchers found that Jedi1 and Jedi2 are specific chemical agonists of Piezo1 and have no effect on Piezo2 (82). Jedi1/2 might act

Table II. Currently reported drugs that regulate Piezo1.

First author/s, year	Category	Drugs	Selectivity	Mechanisms	Inadequacies	(Refs.)
Syeda *et al*, 2015	Agonist	Yoda1	Selective	Binds a hydrophobic pocket located near residues 1961-2063, enhances a twist-tilt-twist like opening motion of the arm, reduces the channel's mechanical activation threshold	Poor solubility in body fluids, cytotoxicity	(76)
Olsen *et al*, 2000	Agonist	Jedi1/2	Selective	Binds the extracellular regions of the peripheral blade, leads to the conformational change	Lacks *in vivo* evidence for Piezo1	(82)
Coste *et al*, 2012	Antagonist	Ruthenium red	Nonselective	Binds two acidic residues, E2495 and E2496, blocks Piezo1-mediated currents from the extracellular side	Lacks *in vivo* evidence for Piezo1	(85)
Coste *et al*, 2010	Antagonist	Gadolinium	Nonselective	Interferes with the adjacent membrane lipids	The specific mechanism is unclear and lacks *in vivo* evidence for Piezo1	(1)
Cox *et al*, 2019	Antagonist	Aβ	Nonselective	Changes the physical and mechanical properties of the membrane	The specific mechanism is unclear and lacks *in vivo* evidence for Piezo1	(87)
Romero *et al*, 2019	Antagonist	Saturated fatty acids	Nonselective	Inhibits Piezo1 currents by increasing the mechanical threshold required for activation	The specific mechanism is unclear and lacks *in vivo* evidence for Piezo1	(89)
Romero *et al*, 2019	Antagonist	Polyunsaturated fatty acids	Nonselective	Modulates the allosteric coupling between the CED and the inner pore helix; alters the interaction between Piezo1 and other proteins	The specific mechanism is unclear and lacks *in vivo* evidence for Piezo1	(89)
Gnanasambandam *et al*, 2017	Antagonist	GsMTx4	Nonselective	Mediates area expansion of the outer leaflet, transfers tension to the fixed-area inner monolayer, potentiates TREK-1 channels	Non-specific interactions with other cation channels	(93)
Evans *et al*, 2018	Antagonist	Dooku1	A selective antagonist of Yoda1	A competitive inhibitor to Yoda1	Poor solubility in body fluids, not directly blocks the channels and the specific mechanism is unclear	(77)
Wang *et al*, 2022	Antagonist	Tubeimoside I	A selective antagonist of Yoda1	Competes with Yoda1 for Piezo1 in the Yoda1 binding sites	Effects depend on the cell type and the concentration of Yoda1	(102)
Pan *et al*, 2022	Antagonist	Salvianolic acid B	A selective antagonist of Yoda1	Competes with Yoda1 for Piezo1 in the Yoda1 binding sites, inhibits cationic current	Does not show selectivity in terms of cell types	(30)

Table II. Continued.

First author/s, year	Category	Drugs	Selectivity	Mechanisms	Inadequacies	(Refs.)
Hong *et al*, 2023	Antagonist	Jatrorrhizine	Selective	Inhibits Yoda1-induced Piezo1 channel activation and the high expression of endothelial mesenchymal transition related molecules caused by Piezo1 activation	The role and mechanism in different cardiovascular diseases and cell subtypes are unclear	(103)
Wang *et al*, 2023	Antagonist	Escin	Selective	Inhibits Yoda1-evoked Ca^{2+} signals in ECs and mechanical stretch-induced activation of NF-κB via Piezo1	The role and mechanism in different cell subtypes are unclear	(105)
Chu *et al*, 2024	Antagonist	Kaempferol	Selective	Inhibits the Piezo1 channels and Ca^{2+} influx, and regulates the downstream pathways of MAPK/NF-κB and Nrf2/HO-1, regulates scavenger receptor CD36-mediated mitochondrial ROS production	The role and mechanism in different cell subtypes are unclear	(39)

Piezo1, Piezo type mechanosensitive ion channel component 1; Aβ, amyloid-β; CED, C-terminal extracellular structural domains; ROS, reactive oxygen species.

through the extracellular regions of the peripheral blade, which is formed by the large region containing residues 1-2,190 (83). Jedi1/2-induced currents activate more rapidly and decay more markedly, whereas Yoda1 activation is slow and irreversible. Jedi1/2 have improved solubility compared to Yoda1 (83). In addition, co-administration of Jedi1 and Yoda1 produce a synergistic activation of Piezo1, suggesting that the two agonists may activate Piezo1 through different binding sites (83). However, there is a lack of animal models or *in vivo* toxicity assessments and follow-up studies are needed to verify efficacy and safety.

Piezo1 antagonists

Ruthenium red (RR) and Gadolinium (Gd^{3+}). RR is an inorganic polycationic dye that has been found to block the binding of Piezo1. The acidic residues E2495 and E2496 of Piezo1, which are located on the inner side of the cell, may be the binding sites of RR (84,85). Gd^{3+} is a trivalent lanthanide that inhibits mechanosensitive ion channels (86). Gd^{3+} has been shown to inhibit Piezo1-mediated mechanosensitive currents (1), although the exact mechanism is not clear. As RR and Gd^{3+} are non-specific Piezo1 inhibitors, they have limited therapeutic applications and are currently used to study Piezo1 function in cells and tissues (5).

Aβ. As aforementioned earlier, Aβ plays an important role in the pathogenesis of Alzheimer's disease and it is an amphiphilic molecule capable of inhibiting the function of Piezo1 by altering membrane structure (87). A study has shown that the L- and D-isomers of monomeric Aβ peptide do not differ in their inhibitory effects on Piezo1, suggesting that Aβ peptide does not regulate the activity of Piezo1 through direct contact with Piezo1, but rather by modulating the cytoskeletal and membrane mechanical properties (88).

Saturated and polyunsaturated fatty acids. Piezo1 channels have three states, from closed to open to inactivated and studies have shown that different fatty acid types affect the different states of Piezo1 (89,90). The saturated fatty acid margaric acid affects the Piezo1 channel from closed to open by increasing the order and bending stiffness of the lipid structure of the cell membrane so that greater mechanical stimulation is required for the activation of Piezo1 (89). In addition, some polyunsaturated fatty acids (PUFA), such as arachidonic acid (AA) and eicosapentaenoic acid (EPA), can inhibit Piezo1 activity by affecting the transition from opening to inactivation of Piezo1 (89). In osteoarthritis, ω3-PUFA has a potential cartilage-protective effect by inhibiting Piezo1/TRPV4 mechanical signaling and modulating membrane properties and inflammatory responses, whereas ω6-PUFA may increase the risk of membrane damage (90). The balanced application of PUFA *in vivo* needs to be further explored to optimize nutritional intervention strategies for osteoarthritis.

GsMTx4. GsMTx4, extracted from the venom of the tarantula spider *Grammostola spatulata*, is the first mechanosensitive channel inhibitor discovered to block endogenous mechanically gated channels (91). Subsequently, GsMTx4 has been shown to reversibly block Piezo1 channel activity (92,93). It is now considered that GsMTx4 also acts by altering local plasma membrane tension rather than by direct contact with Piezo1 (94). GsMTx4 has been widely used in physiological and pathological studies of Piezo1. Studies have shown

that GsMTx4 is able to treat animal models of pulmonary hypertension (95), osteoarthritis (96) and cancer (97), but the development and clinical trials of GsMTx4 as a Piezo1-targeted drug have been hampered by its action on broad cationic mechanosensitive channels (94).

Dooku1. By replacing the pyrazin-2-yl thiadiazole of Yoda1 with a pyrrole-2-yl oxadiazole moiety, researchers discovered a new Piezo1-selective antagonist acting through competitive inhibition of Yoda1; Dooku1 (77). Several studies on the pharmacological activity of Dooku1 have shown that Dooku1 has potential therapeutic effects on a number of diseases. For example, Dooku1 can prevent thrombosis and erythrocyte death associated with sickle cell anemia by decreasing Piezo1-induced Ca^{2+} efflux (98). In addition, inhibition of Piezo1 by Dooku1 is also able to attenuate aortic stenosis (99), regulate brown adipocyte differentiation (100) and reduce neurological deficits after cerebral hemorrhage (101). However, similar to Yoda1, Dooku1 is poorly soluble in body fluids, which to some extent prevents Dooku1 from functioning *in vivo*.

Natural extracts. A number of substances extracted from natural herbs also specifically antagonize Piezo1. Tubeimoside I is a triterpenoid saponin extracted from the Chinese herbal medicine Bolbostemmatis Rhizoma and is currently mostly used in the treatment of a number of types of tumor diseases (102). A study has found that it also competes with Yoda1 for the binding site and inhibits Yoda1 from activating Piezo1 and that this inhibition is selective for Piezo1, but not for other mechanosensitive channels (such as TRPC5, TRPM2 and TRPV4) (36). Salvianolic acid B is a polyphenolic compound extracted from Danshen (*Salvia miltiorrhiza* Bge.). Its mechanism of action is similar to that of Tubeimoside I and it can play a role in the treatment of atherosclerosis (30). The protoberberine alkaloid jatrorrhizine, which is mainly derived from Chinese plants such as Coptidis Rhizoma, used to be commonly used as an anti-inflammatory drug. However, a recent study has found that it can also inhibit Piezo1 activation mediated Ca^{2+} influx, making it a potential drug for treating vasculitis (103). Escin is a mixture of triterpenoid saponins isolated from extracts of the seeds of horse chestnut (*Aesculus hippocastanum* L.), which is currently used clinically for the treatment of chronic venous insufficiency and postoperative edema (104). A study has shown that Escin inhibits the expression of Piezo1-induced inflammatory factors (such as IL-1β and IL-6) in endothelial cells when endothelial cells are subjected to tensile stress, playing an important role in the anti-inflammatory response (105).

Challenges in drug development. Researchers face multiple challenges when developing drugs targeting Piezo1 channels. First, drug selectivity is a key issue. Since Piezo1 is widely expressed in a variety of tissues and cell types, designing a compound that specifically acts on Piezo1 without affecting other ion channels or physiological processes is a challenging task. For example, existing Piezo1 agonists such as Yoda1 and Jedi1/2 have shown activation effects on Piezo1, but their selectivity is not perfect and may interact with other channels or receptors (76,83). Second, the side effects of the drugs are also an important consideration. Since Piezo1 plays an important role in normal physiological functions, such as vascular development, blood pressure regulation and erythrocyte volume control, any interference with these functions may lead to undesirable side effects. Therefore, when developing Piezo1 targeted drugs, it is necessary to carefully evaluate their potential impact on physiological processes and ensure a balance between therapeutic efficacy and potential risks. Pharmacokinetic characterization is also an important aspect in drug development. Understanding how drugs are absorbed, distributed, metabolized and excreted in the body is critical to ensuring their efficacy and safety. Currently, pharmacokinetic studies on Piezo1 channels are inadequate, which limits our understanding of how these drugs function *in vivo*. Therefore, despite the great potential of Piezo1 as a therapeutic target, multiple challenges such as drug selectivity, side effects and pharmacokinetics still need to be overcome in practical development.

6. Conclusion and perspectives

As a novel mechanosensitive cation channel, Piezo1 converts mechanical signals into biological signals to initiate cascaded responses in cellular inflammatory upon imbalance of external mechanical forces and changes in the local cellular environment. Piezo1 further influences the development and regression of inflammation with changes in local mechanical forces during inflammation progression. Chronic inflammation is one that progresses slowly for a long time. It is related to a number of diseases in immune and cardiovascular systems, cancer and diabetes. It is an inflammatory response that endangers the whole body. The present study summarized the role and possible mechanisms of Piezo1 in several common chronic inflammatory diseases, specifically its role in periodontal tissue inflammation and alveolar bone destruction. In addition to the aforementioned diseases, Piezo1 also plays an important role in chronic cystitis (106) and Crohn's disease (75). Therefore, pharmacological modulation of the activity of Piezo1 at the early stage of the disease to inhibit the transduction of mechanical damage signals delays the development of chronic inflammation and improve its prognosis. Due to the wide range of Piezo1 downstream pathways, targeting Piezo1 downstream pathways for the treatment of multiple inflammatory diseases can be investigated in the future. For example, in Crohn's disease Piezo1 exacerbates inflammation through a calcium signaling-mitochondrial damage-NLRP3 pathway cascade, while the NLRP3 pathway plays a role in a variety of chronic inflammatory diseases such as obesity and Parkinson's disease (75). Targeting Piezo1 may be possible to treat patients with comorbid multiple inflammatory diseases.

However, there are a number of challenges and limitations in the design of drugs targeting Piezo1. A number of agonists and antagonists have been identified to directly or indirectly modulate Piezo1 activity, but these drugs are poorly soluble and unstable, making them difficult to use *in vivo*. Due to the wide range of biological functions of Piezo1 in multiple tissues and organs, single activation or inhibition of Piezo1 may produce side effects in addition to therapeutic effects. For example, in AS, inhibition of Piezo1 is not the best treatment because it leads to vasoconstriction and hypertension at the same time (107). These shortcomings prevent drugs that modulate the activity of Piezo1 from being used in clinical

therapy at present. The future direction of disease treatment resides in researches into tissue-specific Piezo1-targeted drugs that achieve ideal therapeutic effects while avoiding potential side effects. In addition to drugs that specifically regulate Piezo1 activity, the use of gene editing techniques enables more precise regulation of Piezo1. A recent study showed that using CRISPR to knock down Piezo1 in a high-grade serous ovarian cancer model interrupted the cascade reaction caused by increased stiffness and activation of Piezo1, slowing down disease progression (108).

In summary, the relationship between Piezo1 and inflammatory diseases is complex. The discovery of Piezo1 provides a new therapeutic target for disease treatment and drugs that regulate its activity have been widely used in basic researches. The role and mechanism of Piezo1 in chronic inflammatory diseases, as well as the development and application of drugs that target Piezo1, may become the focus of future researches.

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Authors' contributions

JY was responsible for writing the original draft, reviewing and editing, validation and conceptualization. CX, XX and JW was responsible for writing the original draft. PS was responsible for writing, reviewing and editing, supervision and project administration. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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