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REVIEW

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PIEZO Ion Channels in Cardiovascular Functions and Diseases

Bertrand Coste, Patrick Delmas

ABSTRACT: The cardiovascular system provides blood supply throughout the body and as such is perpetually applying mechanical forces to cells and tissues. Thus, this system is primed with mechanosensory structures that respond and adapt to changes in mechanical stimuli. Since their discovery in 2010, PIEZO ion channels have dominated the field of mechanobiology. These have been proposed as the long-sought-after mechanosensitive excitatory channels involved in touch and proprioception in mammals. However, more and more pieces of evidence point to the importance of PIEZO channels in cardiovascular activities and disease development. PIEZO channel-related cardiac functions include transducing hemodynamic forces in endothelial and vascular cells, red blood cell homeostasis, platelet aggregation, and arterial blood pressure regulation, among others. PIEZO channels contribute to pathological conditions including cardiac hypertrophy and pulmonary hypertension and congenital syndromes such as generalized lymphatic dysplasia and xerocytosis. In this review, we highlight recent advances in understanding the role of PIEZO channels in cardiovascular functions and diseases. Achievements in this quickly expanding field should open a new road for efficient control of PIEZO-related diseases in cardiovascular functions.

Key Words: angiotensin II ■ atherosclerosis ■ baroreceptor reflex ■ cardiovascular system ■ ion channels ■ red blood cells

All cells in our body are subject to mechanical forces. If gravity constitutes a nonspecific physical constrain, cells present in various tissues experience specific mechanical forces, such as compressive forces generated by external stimuli or skeletal muscle contractions during locomotion, mechanical stress, and strain caused by cyclic distension and contraction of the heart and lungs, or shear stress generated from fluid flows.[1] Cells can also generate endogenous forces such as traction stresses induced by cytoskeletal assembly.[2] These physical constrains are sensed by cells through mechanotransduction, the translation of these forces into biochemical signals, that lead to mechanosensitive feedback critical for cellular functions, organ development, and homeostasis. Since the discovery of mechanosensitive PIEZO ion channels in 2010,[3] hundreds of publications illustrate their fundamental role in physicochemical interactions, morphogenesis, tissue homeostasis, remodeling, and pathogenesis in humans. The discovery of this new class of ion channels has yielded important insights into the mechanisms of somatosensation, as well as other mechano-associated biological processes such as lung volume regulation, bone homeostasis, regulation of urine flow and bladder distention, as well as gastrointestinal motility and development, migration, and proliferation of a variety of cell types (for reviews see Delmas et al,[4] Syeda et al,[5] and Kefauver et al[6]). PIEZO force transducers exist throughout the cardiovascular system and signal to multiple biochemical pathways that have pathophysiological relevance in cardiovascular biology.[7,8] Noticeably, mechanobiology of the cardiovascular system does not rely only on PIEZO channels, and extensive research documented molecular players involved in mechano-signaling pathways in cardiovascular cells including other ion channels, G-protein coupled receptors, adhesion molecules, cytoskeletal components, and a variety of signaling molecules and elements of the extracellular matrix (for detailed review

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Nonstandard Abbreviations and Acronyms

γENaC	epithelial sodium channel γ subunit
AKT1	serine-threonine protein kinase 1, also known as protein kinase B
Ang II	angiotensin II
ASIC2	acid-sensing ion channel 2
AT1	angiotensin II receptor type 1
BP	blood pressure
CALCRL	calcitonin receptor–like
CAMKII	Ca^{2+}/calmodulin-dependent protein kinase II
COMP	cartilage oligomeric matrix protein
DHS	dehydrated hereditary stomatocytosis
ECM	extracellular matrix
eNOS	endothelial NO synthase
GOF	gain-of-function
HDAC4	histone deacetylase 4
ICAM-1	intercellular adhesion molecule-1
MEF2	myocyte enhancer factor 2
mTORC2	mTOR complex 2
NCX1	Na^+/Ca^{2+} exchanger isoform 1
Nedd4-2	neural precursor cell–expressed developmentally downregulated gene 4 type 2
NFAT	nuclear factor of activated T cells
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
PECAM1	platelet endothelial cell adhesion molecule 1
PKA	cAMP-dependent protein kinase
PLA2	phospholipase A2
RBC	red blood cell
TAZ	transcriptional coactivator with PDZ-binding motif
TRPC5	TRP channel classical subtype 5
TSP2	thrombospondin-2
TTN3	tentonin 3
YAP	yes-associated protein

see Davis et al[9]). This review highlights the exciting research on PIEZO channels in cardiovascular functions and diseases.

GENERAL DESCRIPTION OF PIEZO PROTEIN CHANNELS

PIEZO1 and PIEZO2 are widely expressed in a variety of tissues and organs and have been linked to many physiological functions in mammals.[4,5,10] They form prototypical mechanosensitive ion channels with mechanical input acting as the gating stimulus opening a nonselective cationic pore.[3,6,11] Both isoforms share the same general architecture. Each channel is formed by homotrimeric assembly of 3 protein subunits and has a 3-blade propeller architecture topped with a cap that connects to the pore helices (Figure 1).[13–17] Each subunit has 38 transmembrane segments, the first 36 forming one of the surrounding blades, whereas the 2 C-terminal helices associate with those of other subunits to form the central pore module. The inherent mechanosensitivity of PIEZO channels has been demonstrated by reconstituting purified mPIEZO1 into artificial lipid bilayers.[18] The pore module has no force-sensing capabilities,[19] implying that mechanosensitivity is conferred by the flexible blades, each blade being connected to the pore by an intracellular beam (Figure 1).[15,20] Blades have the particularity of being curved, which likely leads to the bowl-shaped configuration of PIEZO-inserted artificial membrane. PIEZO conformational changes and activation were proposed to result from membrane flattening of supported lipid vesicles in response to mechanical stimulus.[16,21] Importantly, the correlation between PIEZO1 activation and blade expansion has been demonstrated using nanoscopic imaging in live cells, in which the plasma membrane directly acts to expand the blades of PIEZO1 at rest potentially conferring exquisite sensitivity to membrane tension (Figure 1).[12] The extracellular cap may be important for setting the inactivation kinetics of PIEZO channels as for providing a physical connection between the blade and the ion-conducting pathway (Figure 1).[21,22]

PIEZOs are multimodal mechanosensitive channels activated by diverse forces, including shear stress, cellular compression, membrane tension, cell swelling, and ultrasounds.[18,23–29] PIEZO channels typically display rapid activation and inactivation kinetics, although the latter may depend on the cellular context and specific membrane mechanical properties.[22,30–32]

PIEZO channels have been reported to interact with some cytoskeletal or extracellular matrix components that may modulate their mechanical sensitivity,[33,34] as well as with MyoD-family inhibitor proteins modulating their gating properties,[32] but no endogenous chemical agonist has been reported to date. However, some pharmacological compounds targeting these channels have emerged and constitute valuable tools to study PIEZO functions. These chemicals allow to directly modulate PIEZO channel activity without using a sophisticated method of mechanical stimulation that often constitutes a technical challenge. A screen of about 3.25 million compounds led to the identification of Yoda1, a PIEZO1 agonist-like molecule conferring activity in the absence of exogenous mechanical stimulation by lowering the pressure sensitivity of the channel.[35] Yoda1 displays a half-maximal effective concentration (EC_{50}) of about 25 μM for human PIEZO1[35] and binds to a

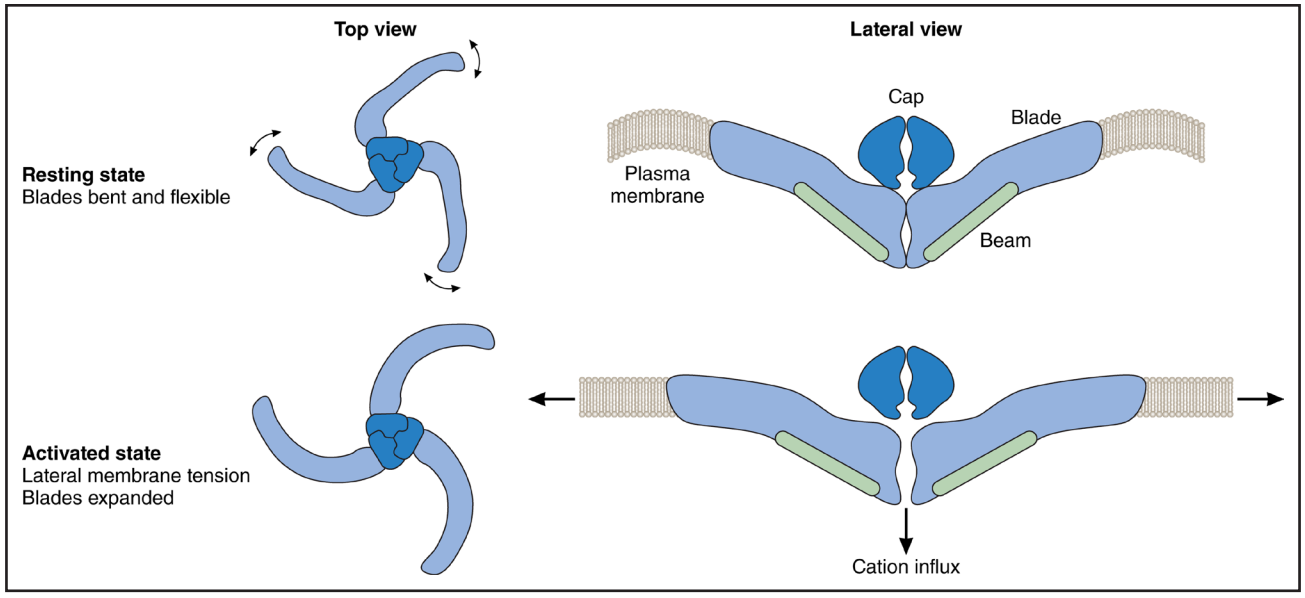

Figure 1. Schematic representation of PIEZO channels in a cellular membrane.
Upper, at rest, the blades of the homotrimeric channel display flexibility. Upon mechanical stimulation (**lower**), the increase in lateral membrane tension causes expansion of the blades, which correlates with channel activation. Adapted from Mulhall et al.[12] Illustration credit: Sceyence Studios.

pocket localized in each of the channel blades, energetically modulating mechanosensory domains and channel gating.[36,37] Yoda1 has poor aqueous solubility at greater concentrations than ≈20 μM[35] but is currently the most widely used chemical activator to study the contribution of PIEZO1 to various biological functions. New pharmacological compounds derived from Yoda1 have been described.[38,39] In addition, Wang et al[40] identified a new set of PIEZO1 chemical activators called Jedi, although with low potencies (EC_{50}≥150 μM), limiting their use in exploratory experiments. Future challenges in drug discovery for PIEZO channels are the development of agonists targeting PIEZO2, as well as the identification of specific blockers of PIEZO1 and PIEZO2. Indeed, these channels are blocked by some trivalent cations and by the multivalent cationic compound ruthenium red,[3] which are nonselective inhibitors of cationic channels, as well as by the GsMTX-4 (grammostola mechanotoxin #4) spider toxin,[41] an amphipathic peptide acting by inserting into the membrane and affecting mechanosensitive channels nonspecifically.[42]

EXPRESSION OF PIEZO1 AND PIEZO2 IN HUMAN CARDIOVASCULAR CELLS

As pivotal mechanosensors, PIEZO proteins are found in organisms from unicellular protists and plants to vertebrates and mammals.[3] PIEZO1 in mammals is mainly expressed in non-neural tissues, with particularly high expression in the lung, bladder, kidney, and skin, whereas PIEZO2 channel is predominantly present in sensory cells, such as trigeminal and dorsal root ganglion sensory neurons and Merkel cells, where its deletion leads to deficits in touch sensation and proprioception.[3,43–45] There is increasing evidence of the expression of PIEZO proteins in cardiovascular cells, including endothelial cells (ECs), cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells. PIEZO1 expression in the endothelium and endocardium starts between embryonic day (E)9 and E10.5.[27,29] Mice with constitutive PIEZO1 inactivation show major pericardial effusion and embryo died at midgestation. These mice lacked major blood vessels and had disorganized embryonic vasculature, suggesting the importance of PIEZO1 in early vascular development.[27,29] Moreover, specific invalidation of *PIEZO1* in mouse ECs causes damaged lymphatic valve formation in mice.[46,47] By contrast, *PIEZO2* gene is expressed in neurons of the nodose-petrosal-jugular ganglia, where it participates in the baroreceptor reflex in mice.[48] In summary, these studies set a major role for PIEZO1 channels in non-neuronal cardiovascular cells, while PIEZO2 appeared restricted to nerve cells. Of note *PIEZO1* mRNA is highly expressed in the sinoatrial node, the primary pacemaker of the heart, but PIEZO1 role has yet to be determined. Altered hemodynamic load can modulate the activity of the sinoatrial node through the Bainbridge reflex, also called the atrial reflex, which occurs when the heart rate increases in response to a rise in atrial pressure.[49]

Single-cell databases from human cardiovascular tissues accord well with data in mice. *PIEZO1* transcript was found to be ubiquitous in cardiovascular cells, including vascular ECs, vascular fibroblasts, vascular smooth muscle cells, and erythroids, although difference could be observed between cell types (Figure 2). Highest level

(≈50 normalized transcripts per million [nTPM]) is found in vascular ECs, which represents a level of expression close to those observed in highest *PIEZO1* expressing tissue types, for example, breast ECs (102.8 nTPM), adipose tissue adipocytes (96.7 nTPM), and ovary lymphatic ECs (92 nTPM: https://www.proteinatlas.org/). *PIEZO2* transcripts are hardly detectable in human cardiovascular cells. However, it should be kept in mind that the correlation between mRNA levels and protein abundance was not observed in many studies on human tissues.[51]

ROLE OF PIEZOS IN THE VASCULATURE

PIEZO1 Transduces Hemodynamic Forces to Regulate EC Homeostasis and Vascular Function

A monolayer of ECs lines the inner surface of all blood vessels (arteries, capillaries, and veins). EC functions are regulated by chemical mediators such as hormones, cytokines, and neurotransmitters, as well as mechanical stress produced by hemodynamic forces.[52] Indeed, ECs constantly experience shear stress at their surface, a tangential force exerted by circulating blood that can arise from laminar or disturbed flow, as well as stretch induced by cyclic strain due to pulsatile change in blood pressure (BP; Figure 3). Under normal conditions, a dynamic balance between hemodynamic forces and biological responses maintains endothelial integrity, whereas perturbation of blood flow that occurs with atherosclerosis or hypertension leads to vascular remodeling and dysfunction.[56–59] ECs are equipped with many mechanosensors or responsive microdomains, such as cell-cell junctional proteins and adhesion molecules, receptors, ion channels, membrane microdomains, and glycocalyx, which sense and transduce hemodynamic forces to regulate EC homeostasis and vascular function,[60] among which PIEZO1 emerges as a key player. Indeed, PIEZO1 channels are present both in the apical endothelial membrane and at the inter-endothelial junction complexes where they interact with PECAM1 (platelet EC adhesion molecule-1).[27,29,61] At these sites, PIEZO1 channels are activated by shear stress and could sense stretch/membrane tension, respectively. Constitutive PIEZO1 ablation in mice causes embryonic lethality before E14.5 due to impaired vasculature development and defective circulation, including vasculature disorganization and major pericardial effusion.[27,29] Importantly, specific invalidation of *PIEZO1* in endothelium also leads to embryonic or early postnatal lethality pointing out that this phenotype is caused by lack of PIEZO1 in ECs.[27,47] This illustrates PIEZO1's pivotal role in the development of the cardiovascular system in mammals. In zebrafish, PIEZO1 has also been shown to coordinate the outflow tract valve formation by driving the response to hemodynamic forces. Indeed, PIEZO1 modulates Kruppel-like factor 2 and Notch activity in the endothelium and Yap1 (yes-associated protein 1) localization in smooth muscle progenitors.[62] All these factors are necessary for outflow tract valve morphogenesis in vivo in response to mechanical forces. Inactivation of *PIEZO1* leads to defective outflow tract and aortic valve development.[62,63]

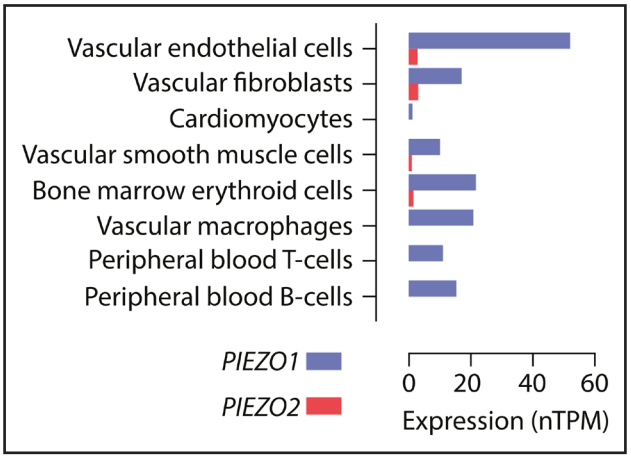

Figure 2. Expression of *PIEZO1* and *PIEZO2* transcripts in cardiovascular-related cells in humans.
PIEZO1 transcripts are detected in virtually all cell types. The lowest level is seen in cardiomyocytes. *PIEZO2* displays low expression in vascular fibroblasts and endothelial cells, and no detectable expression in other cardiovascular and blood cells. Data extracted from the Human Protein Atlas (https://www.proteinatlas.org/), based on meta-analysis of literature on single-cell RNA sequencing and single-cell databases that include healthy human tissues.[50] nTPM indicates normalized transcripts per million.

Shear stress and cyclic strain on ECs are involved in numerous biological functions such as cell shape and orientation, proliferation and apoptosis, vascular tone modulation, antithrombotic activity, production and elimination of reactive oxygen species, and gene expression changes.[9] Since PIEZO1 acts as the upstream initiator of many force-related signalization pathways, accumulating evidence documents its crucial role in EC functions. However, deciphering the endothelial functions of PIEZO1 is complexified by EC heterogeneity among organs and vessel types.[64] Characterization of PIEZO1 signaling pathways in ECs from diverse origins shows that the vascular bed specificity is crucial regarding PIEZO1 functions in endothelium. An illustration of this specificity comes from PIEZO1's contribution to performance during exercise. As fluid flow increases, endothelial PIEZO1 contributes to the constriction of mesenteric resistance arteries with the purpose of directing the blood flow away from the gastrointestinal tract, but this effect of endothelial PIEZO1 is absent in saphenous and carotid arteries supplying blood in legs and brain, respectively.[65]

PIEZO1 Regulates Adherens Junctions at Endothelial Barrier

An important function of endothelial PIEZO1 channels is their contribution to alignment of ECs to the direction of fluid flow[27,29,66] and adherens junction

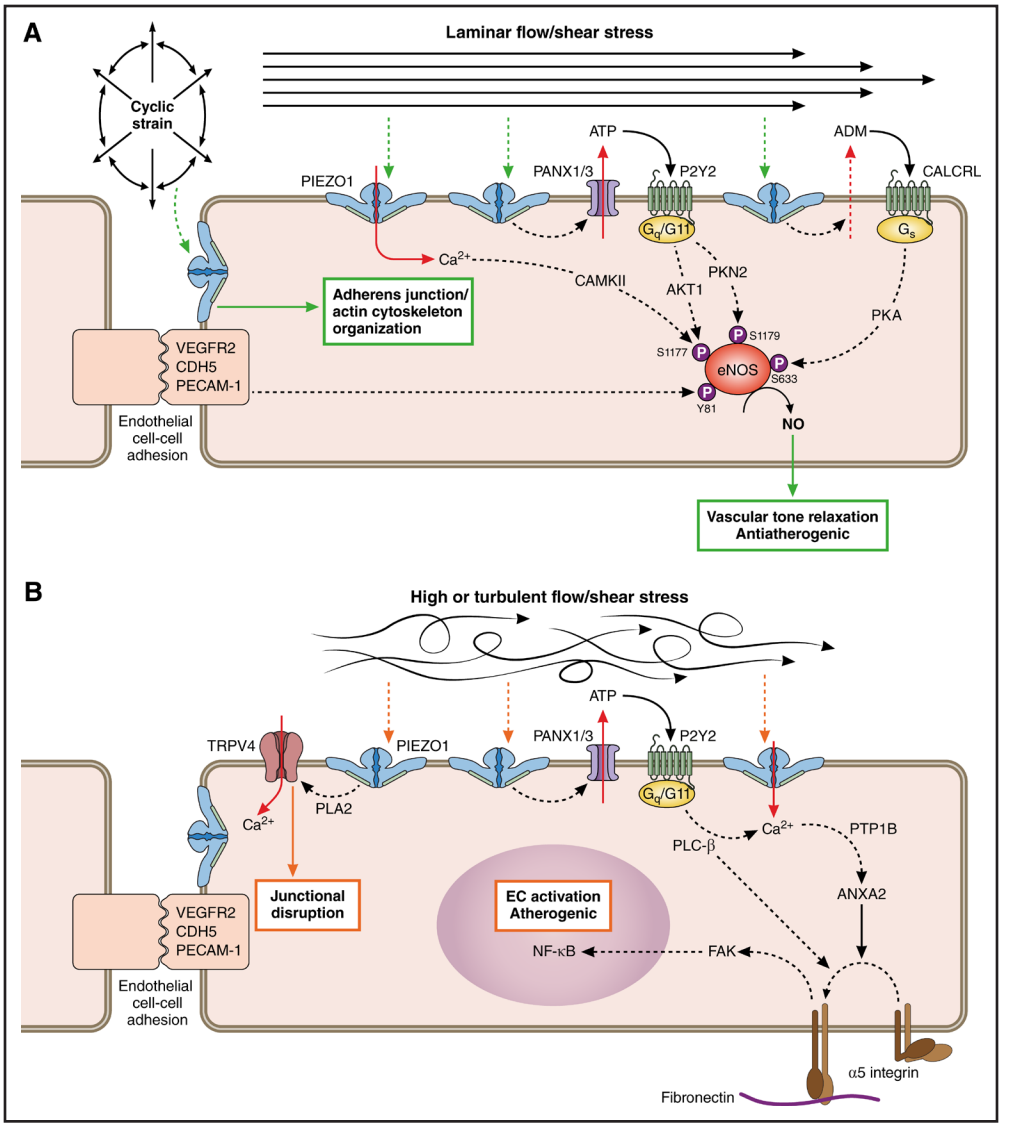

Figure 3. Functions of PIEZO1 in adult vascular endothelial cells (ECs).
A, Under physiological conditions, several signaling pathways initiated by PIEZO1 mechanotransduction of shear stress or cyclic strain forces lead to the phosphorylation of eNOS (endothelial NO synthase) at various positions, leading to the production of NO. NO diffusion induces many physiological responses, including vascular tone relaxation and atheroprotection. **B**, Under pathological conditions, abnormal activation of PIEZO1 by high or disturbed blood flow induces $[Ca^{2+}]_i$ increase (through PIEZO1 and synergically through PANX/P2Y2/PLC-β [phospholipase C beta] signaling) leading to ANXA2 (annexin A2) dephosphorylation by PTP1B (protein tyrosine phosphatase 1B). ANXA2 binds directly to α5-integrin and promotes its translocation to lipid rafts.[53] Other putative pathways downstream of PLC-β activation may contribute to integrin translocation.[54] Then, binding of fibronectin to integrin leads to FAK (focal adhesion kinase)/NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation and atherogenic response. Abnormal activation of PIEZO1 is also involved in PLA2 (phospholipase A2)-dependent activation of TRPV4 (transient receptor potential cation channel subfamily vanilloid member 4), causing sustained $[Ca^{2+}]_i$ elevation responsible for disruption of adherens junctions and actin remodeling.[55] ADM indicates adrenomedullin; AKT1, serine-threonine protein kinase 1, also known as protein kinase B; $[Ca^{2+}]_i$, intracellular calcium concentration; CDH5, cadherin 5; CALCRL, calcitonin receptor-like; Gq/G11, G protein alpha subunits q/11; PANX1/3, pannexins 1/3; P2Y2, purinergic receptor P2Y; PECAM, platelet endothelial cell adhesion molecule; PKA, cAMP-dependent protein kinase; PKN, serine/threonine protein kinase N; and VEGFR, vascular endothelial growth factor receptor. Illustration credit: Sceyence Studios.

dynamics.[55,61,67,68] By initiating localized force-dependent Ca^{2+} entry at cell-cell junction, PIEZO1 channels participate in the formation and remodeling of adherens junctions.[61] PIEZO1 channels are also required for leukocyte diapedesis, the movement of leukocytes out of the vascular system.[67] Leukocyte-induced clustering of ICAM-1 (intercellular adhesion molecule-1) at EC surface generates mechanical forces that synergize with low shear stress to activate endothelial PIEZO1. Subsequent downstream signaling leads to endothelial barrier opening and leukocyte extravasation.[67] In pathological conditions, such as increased lung microvessel pressure, endothelial PIEZO1 activation leads to calpain-induced disruption of vascular endothelial–cadherin adhesion.

This induces endothelial barrier disruption and promotes edema formation.[68] Moreover, in human umbilical vein ECs, high and prolonged shear stress stimulation of PIEZO1 leads to TRPV4 (transient receptor potential cation channel subfamily Vanilloid member 4) channel opening via activation of PLA2 (phospholipase A2). The resulting TRPV4-dependent sustained intracellular Ca^{2+} elevation is responsible for disruption of the adherens junctions and actin remodeling.[55] Therefore, PIEZO1 can act upstream of TRPV4 to induce pathological events. The functional coupling between PIEZO1 and TRPV4 characterized in human umbilical vein ECs is likely dependent on the vascular bed, as activation of PIEZO1 or TRPV4 in hepatic portal vein ECs have opposing independent effects promoting relaxation and contraction, respectively.[69]

PIEZO1 Regulates Endothelial NO Production

Many physiological vascular consequences downstream of endothelial PIEZO1 activation depend on NO production, which is a major regulator of vascular homeostasis. eNOS (endothelial NO synthase) is the main source of endothelium-derived NO and is activated by a myriad of signaling pathways downstream of receptor activation by vasoactive ligands as well as hemodynamic forces such as shear stress.[70] PIEZO1 plays a pivotal role in the conversion of hemodynamic forces to biological signals leading to eNOS activation by posttranslational modifications (Figure 3A). Endothelial PIEZO1 activation can initiate several independent pathways leading to eNOS phosphorylation at different sites that can act synergistically to increase NO production (Figure 3A). By cooperating with Pannexin channels, endothelial PIEZO1 mediates flow-induced ATP release and subsequent auto/paracrine activation of Gq/G11-coupled P2Y2 receptors.[71] This pathway leads to the activation of protein kinase N2 that mediates direct phosphorylation of eNOS at serine 1179, as well as activation of the AKT1 (serine-threonine protein kinase 1, also known as protein kinase B) synergistically with mTORC2 (mTOR complex 2), which in turn mediates phosphorylation of serine 1177.[71,72] In addition, phosphorylation of serine 1177 has been suggested to occur via PIEZO1-dependent CAMKII (Ca^{2+}/calmodulin-dependent protein kinase II) activation.[33] Endothelial PIEZO1 also initiates flow-induced adrenomedullin release and subsequent auto/paracrine activation of CALCRL (calcitonin receptor–like) receptor, leading to Gs-mediated increases in cAMP levels and resulting in PKA (cAMP-dependent protein kinase)-dependent eNOS phosphorylation of serine 633.[73] Moreover, Yoda1 activation of PIEZO1 has been shown to promote tyrosine 81 phosphorylation of eNOS.[74] Therefore, endothelial PIEZO1 activation initiates multiple pathways that enhance NO production and contributes to vascular tone homeostasis.

An illustration of endothelial PIEZO1-eNOS axis involvement in vascular homeostasis is its implication in stabilizing muscle capillary density.[75] In muscle, endothelial PIEZO1 activation of eNOS induces NO production and diffusion to adjacent pericytes, where it leads to inhibition of TSP2 (thrombospondin-2) production, an inducer of EC apoptosis. Consequently, endothelial PIEZO1 activity increases the stability of microvascular endothelium.[75] Endothelial PIEZO1 has also been shown to interact with the COMP (cartilage oligomeric matrix protein) via its C terminus. COMP is a matricellular glycoprotein that protects against endothelial dysfunction in hypertension. Its interaction with PIEZO1 regulates endothelium-dependent relaxation and BP by increasing PIEZO1 activity and in fine NO production.[33]

Pathogenic Effects of Endothelial PIEZO1 Activity Under Disturbed Flow

Its pivotal function as a hemodynamic force sensor not only confers endothelial PIEZO1 a critical role in maintaining physiological homeostasis under laminar flow but also in the development of vascular pathologies under high or turbulent flow (Figure 3B). It has been reported that PIEZO1 is upregulated in pulmonary arterial ECs during pulmonary hypertension,[76] and pharmacological manipulation of its activity has been reported to modulate vascular defects induced in models of vascular calcification,[77] hyperglycemia,[78] and pulmonary hypertension.[79] Moreover, PIEZO1 is directly involved in atherosclerosis,[54] a common condition corresponding to a slowly worsening chronic inflammatory disease (Figure 3B). Atherosclerosis occurs preferentially in branches and curves in arteries exposed to disturbed blood flow inducing inflammation, endothelial-mesenchymal transition, thrombosis, vasoconstriction, and barrier dysfunction.[80] Atherosclerosis is characterized by a buildup of plaque made up of deposits of lipids and cellular waste products in the inner lining of the arteries. Consequently, the arteries become thickened, stiff, and narrow, reducing blood flow and oxygen supply to the vital body organs and extremities and is the pathological basis of many cardiovascular diseases. Interestingly, PIEZO1 drives opposite effects under laminar or disturbed flow. Indeed, signaling initiated by PIEZO1, the purinergic P2Y2 receptor, and Gq/G11 activation, which under laminar flow results in atheroprotective eNOS activation, leads to atheroprone inflammatory signaling involving α5 integrin–dependent NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation under disturbed flow.[54] Still under disturbed flow, PIEZO1-Ca^{2+} activation of protein tyrosine phosphatase 1B leads to annexin A2 dephosphorylation and binding to integrin $\alpha5\beta1$, promoting its translocation and activation, again constituting an atheroprone signaling.[53]

Although laminar and disturbed flow both initiate calcium influx through PIEZO1 channels, what controls the respective activation of antiatherogenic or proatherogenic pathways remains to be determined. Recently, abnormal expression of PIEZO1 was found to be implicated in EC autophagy in a mouse model of atherosclerotic plaque growth.[81] Autophagy mechanisms within the ECs have an essential role in maintaining physiological characteristics, whereas defective autophagy promotes endothelial proinflammatory and atherogenic phenotypes. It was suggested that PIEZO1 contributes to EC autophagy defects by promoting activation of the YAP, a transcriptional coactivator in the Hippo pathway.[81] Therefore, targeting PIEZO1 may constitute a therapeutic approach in defective autophagy to restore endothelial function in atherosclerosis.

Endothelial PIEZO1 Senses Oscillating Shear Stress in the Lymphatic System

Endothelial PIEZO1 also senses oscillating shear stress in the lymphatic system and integrates mechanical signals into a genetic program that regulates lymphatic valve development and maintenance,[46,47] as well as lymphatic expansion in response to fluid flow.[82] A recent study reported that increased intracranial pressure and diminished cerebrospinal fluid flow, observed in a craniosynostosis mouse model, are associated with pathological changes to meningeal lymphatic vessels that affect their sprouting, expansion, and long-term maintenance.[83] Remarkably, Yoda1 treatments can reduce intracranial pressure and help restore meningeal lymphatic vessel functions and brain–cerebrospinal fluid perfusion. Yoda1 treatment outcome could result from the combination of vascular PIEZO1 activation regarding intracranial pressure reduction and lymphatic PIEZO1 activation concerning meningeal lymphangiogenesis.

In humans, homozygous or compound heterozygous loss-of-function PIEZO1 variants cause generalized lymphatic dysplasia. The severity of phenotypes associated with loss-of-function PIEZO1 mutations in patients covers a wide range, with clinical manifestations including fetal hydrops, hydrocele, pleural effusion, varicose veins, lymphedema, and chylothorax.[84–86]

ROLE OF PIEZOS IN THE HEART

PIEZO1 in Cardiac Fibroblasts and Cardiomyocytes

The above findings clearly indicate that shear stress activation of endothelial PIEZO1 is required for the proper development of blood and lymphatic vessels.[27,29,46,47] However, the expression of PIEZO proteins is not restricted to ECs. Recent studies highlight the emerging significance of PIEZO1 function in both human and mouse cardiac fibroblasts.[87,88] Cardiac fibroblasts play a pivotal role in preserving myocardial function and integrity of the heart tissue after injury and sense changes to the cardiac environment through mechanical cues. Altered mechanical environment of cardiac fibroblasts, secondary to fibrosis, cardiac dilatation, or hemodynamic changes in heart failure, causes fibroblast-to-myofibroblast transdifferentiation with enhanced expression of ECM (extracellular matrix) proteins.[89] Excess of cardiac ECM increases the stiffness of the myocardium, reduces pumping capacity, and leads to cardiac remodeling.[90,91] Yoda1 effects on cardiac fibroblasts indicated that PIEZO1 activation increases both mRNA levels and protein secretion of the prohypertrophic and profibrotic cytokine IL (interleukin)-6 through p38 mitogen-activated protein kinase downstream of Ca^{2+} entry.[88] Thus, cardiac fibroblasts express mechanically activated PIEZO1 channels coupled to the paracrine secretion of IL-6, a mechanism potentially important in regulating cardiac remodeling. In the same vein, Emig et al[87] described a role for PIEZO1 in increasing atrial fibroblast cell stiffness. Using overexpression and siRNA studies, they showed that PIEZO1 was instrumental for fibroblast adaptation to changes in matrix stiffness and that PIEZO1-induced cell stiffening could be transmitted in a paracrine manner to neighboring (nontransfected) cells by a signaling mechanism requiring the profibrotic cytokine IL-6. Together, these recent studies identify PIEZO1 as a new candidate for targeted interference with cardiac fibroblast function and highlight its emerging role in pathological cardiac remodeling in vivo.

The importance of PIEZO1 in structural remodeling was initially put forward by Retailleau et al[92] while investigating the role of stretch-activated ion channels in arterial smooth muscle cells. Remodeling of small-diameter arteries is a structural adaptation of the vessel wall to hemodynamic stimuli[93] and is linked to cardiovascular morbidity and mortality.[94,95] Retailleau et al[92] found that smooth muscle PIEZO1 was required for stretch-activated ion channel activity and cytosolic calcium increase and had a trophic effect on resistance arteries, influencing both diameter and wall thickness in hypertension. Because arterial remodeling is recognized as a major prognostic marker in patients at high cardiovascular disease risk, PIEZO1 might be considered a new strategic target in the treatment of hypertensive conditions.[94,95]

The cardiomyocytes constitute between one-third and a half of the total cardiac cell population and are responsible for the contractile forces of the heart. Although initial studies have reported relatively low level of *PIEZO1* mRNA expression in heart tissues and cardiomyocytes (see Figure 2),[88,96] recent evidence indicates that PIEZO1 protein is expressed in the sarcolemma of adult cardiomyocytes, where it may serve as a mechano-chemo transducer activating Ca^{2+} and reactive oxygen

species signaling[97] or regulating eNOS expression.[98] Either cardiac-specific knockout or overexpression of PIEZO1 in mice results in defective Ca^{2+} and reactive oxygen species signaling and the development of cardiomyopathy, suggesting a homeostatic role of PIEZO1 in cardiac functions.[97] Expression of PIEZO1 was found to be upregulated by real-time polymerase chain reaction, Western blot, and immunohistochemistry analysis in a heart failure model established by the induction of left anterior descending coronary artery ligation in rats.[96] Expression of PIEZO1 was enhanced by Ang II (angiotensin II) in neonatal rat ventricular myocytes via AT1 (Ang II receptor type 1) receptor-Erk1/2 signal pathways. Consistent with this, AT1 receptor blocker therapy (losartan treatment) in vivo prevented PIEZO1 protein upregulation in failure heart,[96] indicating that AT1 receptor activation may be responsible for PIEZO1 upregulation in cardiomyocytes during heart failure.

Consistently, PIEZO1 malfunctioning has been linked with pathological left ventricular hypertrophy secondary to pressure overload.[99] Prior studies have identified 2 main stimuli for triggering left ventricular hypertrophy, the activation of the Gq-coupled AT1 receptor and mechanical forces such as pressure overload.[100] These stimuli are known to activate the hypertrophic signaling cascades, including the calcineurin-NFAT (nuclear factor of activated T cells)-GATA4 pathway and the CaMKII-HDAC4 (histone deacetylase 4)-MEF2 (myocyte enhancer factor 2) pathway.[101–103]

An unanswered question therefore remained the identification of the molecular mechanical sensor that detects changes in mechanical load and transduces it into activation of the hypertrophic signaling cascade. PIEZO1 was recently found to be upregulated under pressure overload and enriched near T-tubule and intercalated disc of cardiomyocytes.[104] By using cardiac conditional PIEZO1 KO mice undergoing transverse aortic constriction, it was demonstrated that PIEZO1 was required for the development of cardiac hypertrophy and subsequent adverse remodeling. Mechanistically, it was proposed that PIEZO1 perturbed calcium homeostasis, mediating extracellular Ca^{2+} influx and intracellular Ca^{2+} overload, thereby increasing activation of the Ca^{2+}-dependent signaling.[104] Yu et al[99] further demonstrate that deletion of PIEZO1 in cardiomyocytes prevents activation of the CaMKII-HDAC4-MEF2 pathway in the transverse aortic constriction–induced pressure overload model and that this effect was associated with significant inhibition of the hypertrophic response to pressure overload (Figure 4). In addition, loss of PIEZO1 prevents the altered expression of critical calcium handling proteins previously associated with pressure overload-induced left ventricular hypertrophy, including TRPM4 and the NCX (Na^+/Ca^{2+} exchanger isoform 1).[105,106] Thus, the Ca^{2+}-permeable PIEZO1 transduces increased myocardial forces caused by pressure overload and initiates the hypertrophic signaling cascade resulting in pathological left ventricular hypertrophy.

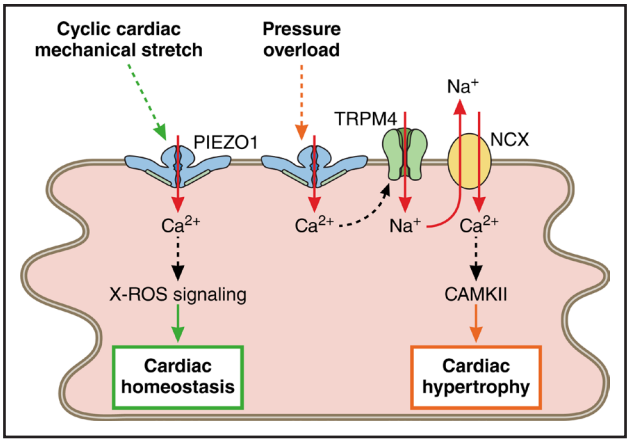

Figure 4. PIEZO1 activates hypertrophic signaling pathway in cardiomyocytes.
Pressure overload activates PIEZO1 in cardiomyocyte plasma membrane, increasing local $[Ca^{2+}]_i$ that in turn activates the Na^+-permeable TRPM4 (transient receptor potential cation channel subfamily Vanilloid member 4) channel. The resultant increase in local $[Na^+]_i$ is expected to increase Ca^{2+} entry via the NCX1 (Na^+/Ca^{2+} exchanger isoform 1), thus amplifying the calcium signal initiated by PIEZO1. Calmodulin may respond to this high-amplitude Ca^{2+} signal and activate the CAMKII (Ca^{2+}/calmodulin-dependent protein kinase II)-dependent (CaMKII-HDAC4 [histone deacetylase 4]-MEF2 [myocyte enhancer factor 2]) hypertrophic signaling pathway. PIEZO1 channel also converts mechanical stretch of cardiomyocytes into Ca^{2+} and reactive oxygen species (ROS) signaling, maintaining normal heart function. Illustration credit: Sceyence Studios.

ROLE OF PIEZOS IN THE KIDNEY

PIEZO1 or PIEZO2 as Mechanosensors in Renin-Producing Cells?

The renin-angiotensin-aldosterone system is a critical regulator of cardiac, vascular, and renal physiological functions through the regulation of vascular tone and water and salt homeostasis.[107,108] In addition, the renin-angiotensin-aldosterone system has implication in pathophysiological conditions, such as hypertension, heart failure, and renal diseases.[109] Renin secretion from the juxtaglomerular apparatus is a rate-determining factor of the renin-angiotensin system, which controls BP and body fluid balance.[108] Renin is produced and secreted by the renal juxtaglomerular cells, which are located in the media of the afferent arterioles at the entrance to the glomerulus.[110] Renin release from juxtaglomerular cells is modulated in an inverse fashion by the BP inside the afferent arterioles. It is thought that perfusing pressure of the afferent arterioles stimulates the juxtaglomerular cells, driving calcium influx and suppressing renin secretion, whereas volume depletion relaxes the arteriole, preventing calcium influx to stimulate renin secretion.[111–113] Consistently, an increase in mechanical stress and calcium influx is known to inhibit forskolin-induced renin secretion in primary juxtaglomerular cells.[114] However, the detailed mechanisms by which mechanical stress regulates the synthesis and secretion of renin remain unclear. Recent

studies have provided contradictory results concerning the role of PIEZO1 and PIEZO2 in juxtaglomerular cells. Yang et al[115] showed that PIEZO1, but not PIEZO2, is functionally expressed in juxtaglomerular cells, activation of which increases intracellular calcium level and results in decreased levels of renin synthesis and secretion. Calcium mobilization induced by mechanical stress using microfluidics is reduced in PIEZO1-KO juxtaglomerular cells,[115] yet not completely abolished, suggesting that other proteins, including TRPV4,[116] may also contribute to mechanosensation. Mechanistically, the Ptgs2 (COX-2)-PGE2-EP1/3 (prostaglandin-endoperoxide synthase 2/cyclooxygenase 2 PGE2 receptor 1/3) pathway has been proposed to mediate PIEZO1 activation-induced renin downregulation. Further in vivo studies in mice indicated that activation of PIEZO1 by Yoda1 downregulates renin expression and decreases the mean BP level, while adeno-associated virus–mediated PIEZO1 knockdown in the kidney abrogates the effects of Yoda1.[115] Together, these results revealed that the activation of PIEZO1 in juxtaglomerular cells decreases renin expression and regulates BP, highlighting its therapeutic potential as a drug target of the renin-angiotensin system.

At variance, Mochida et al[117] found that PIEZO2 was expressed in glomerular mesangial cells and renin-producing juxtaglomerular cells at both the mRNA and protein levels. Prior single-cell RNA sequencing of mouse glomerular cells showed that PIEZO2 was expressed at low levels in juxtaglomerular cells.[118] In response to the reduction of mechanical load to the glomeruli by dehydration, PIEZO2 expression was found to be downregulated in mesangial cells and markedly upregulated in juxtaglomerular cells, along with the overproduction of renin. In addition, the expression of the renin-coding gene *Ren1* was reduced by PIEZO2 knockdown in cultured juxtaglomerular As4.1 cells.[117] These data suggest that PIEZO2 function promotes renin production. This result was unexpected given that renin expression and release from juxtaglomerular cells are suppressed by Ca^{2+} influx, a phenomenon known as the calcium paradox of renin secretion.[116] In summary, these studies suggest that PIEZO proteins play an important role in the mechanosensation of juxtaglomerular cells and contribute to BP homeostasis by regulating renin synthesis and secretion. However, further research will be needed to clarify the specific role of PIEZO1 and PIEZO2 in these seemingly contradictory results.

ROLE OF PIEZOS IN BLOOD CELLS

PIEZO1 Contributes to Volume Regulation of Red Blood Cells

Red blood cells (RBCs) display a unique biconcave shape exposing maximal surface area for rapid O_2 and CO_2 exchanges across the capillary walls.[119] They deform, fold, squeeze, and are exposed to mechanical stresses in various levels of the circulatory system (shear stress, turbulence, contact/collision to foreign surfaces). For instance, to navigate narrow capillaries, RBCs decrease their cell volume to facilitate passage. Their deformability depends on the interplay between cytoskeletal components, integral transmembrane protein complexes, and intracellular viscosity.[120] Defects in RBC mechanical stability can lead to RBC damage and ultimately disruption of cell membrane releasing hemoglobin (ie, hemolysis).[121] Although PIEZO1 is present only at a few hundred copies per cell,[122,123] it functions as a major determinant of RBC volume regulation, contributing to their mechanical stability. This role is illustrated by *PIEZO1* knockdown in zebrafish[124] and *PIEZO1* blood cell–specific genetic deletion in mice, in which RBCs are overhydrated and exhibit increased fragility (Figure 5).[125] Similarly, PIEZO1 hypomorphic variants in humans lead to overhydrated RBCs.[126] However,

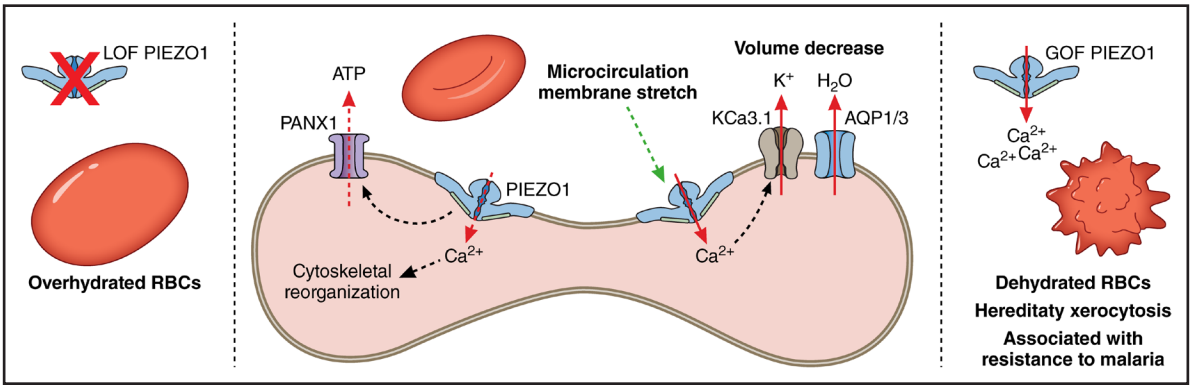

Figure 5. PIEZO1 regulates volume of red blood cells.
Membrane stretch of red blood cells (RBCs) in narrow capillaries activates Ca^{2+} signals through PIEZO1, which in turn evokes K^+ efflux through KCa3.1 and water efflux through aquaporins. This leads to volume decrease to facilitate passage. PIEZO1 Ca^{2+} influx also potentially contributes to dynamic cytoskeletal reorganization and ATP release through PANX1 (pannexin 1). Gain-of-function or loss-of-function (GOF or LOF) mutations of PIEZO1 lead to dehydrated or overhydrated RBCs, respectively. AQP1/3 indicates aquaporin 1/3; and KCa3.1, calcium dependent potassium channel 3.1. Illustration credit: Sceyence Studios.

other PIEZO1 mutations in humans lead to hereditary xerocytosis, also called dehydrated hereditary stomatocytosis (DHS), a congenital hemolytic disorder characterized by dehydrated RBCs (Figure 5).[127–132] Functional testing of the activity of several mutant channels linked to DHS reveals that they lead to increased signal (and calcium entry) for a given stimulus compared with wild-type channels. Thus, DHS results from gain-of-function (GOF) mutations in PIEZO1 channels.[127,128] In conclusion, excess or loss of PIEZO1 activity in RBCs leads to dehydration or overhydration of RBCs, respectively, highlighting the key role of PIEZO1 in maintaining RBC volume homeostasis.

Mechanistically, PIEZO1 and KCa3.1, also known as the GARDOS channel, participate together in the volume regulation of circulating RBCs (Figure 5).[123] In narrow capillaries and sinusoids, the increased mechanical constraint on RBCs triggers calcium entry through PIEZO1, which in turn activates the calcium-dependent KCa3.1, leading to K^+ efflux and subsequent water loss. This coupling mechanism induces temporary decrease in cell volume to facilitate passage in microcapillaries.[125,133] In addition to KCa3.1 channel activation, calcium mobilization caused by PIEZO1 in RBCs also contributes to shear stress–induced ATP release possibly through Pannexin 1.[134] Interestingly, prior studies in RBCs have linked Ca^{2+} signaling to the regulation of interaction between junctional proteins and the membrane cytoskeleton,[135] suggesting that PIEZO1 could be involved in the dynamic organization of RBCs essential for maintaining their biconcave shape and mechanics.[136] Moreover, PIEZO1 activation by Yoda1 induces RBC-NOS activation and NO production in human erythrocytes, which can mimic shear stress–induced NO production by RBCs.[137] RBC-NOS has been shown to contribute to BP homeostasis in mice.[138]

In addition to controlling volume and hydration homeostasis in mature RBCs, PIEZO1 is involved in erythropoiesis. Myelodysplastic features, including symptomatic anemia, have been reported in humans displaying PIEZO1 mutations.[139] PIEZO1 is expressed in early progenitor cells, and its chemical activation delays erythroblastic and reticulocyte maturation.[140,141] Of note, PIEZO1 GOF mutations linked to DHS induce maturation impairments of RBCs.[140,141]

PIEZO1-Induced RBC Dehydration Protects From *Plasmodium falciparum* Infection

The causative parasite for malaria, *Plasmodium*, has exerted strong evolutionary pressure on the human genome by selecting polymorphisms conferring protection to the disease. Moreover, variations in RBC hydration and volume are associated with *Plasmodium falciparum* growth rate.[142,143] A PIEZO1 GOF mutation introduced in mouse, in addition to recapitulating human hereditary xerocytosis phenotype including RBC dehydration, confers protection against experimental cerebral malaria.[144] In line with this, a comparative genomics approach led to the identification of a PIEZO1 GOF mutation, E756del, present at high incidence in African people (about one-third of individuals) and associated with protection against severe malaria.[144,145] RBCs from E756del carriers confer a protective effect in vitro against infection by *P falciparum* by a mechanism that could be related to reduced infection or impaired export of virulence proteins.[144,145] In healthy RBCs, pharmacological activation of PIEZO1 inhibits *P falciparum* invasion likely by changing RBC shape and surface-volume ratio.[146,147] Achieving specific PIEZO1 activation in RBCs could constitute a challenging but promising antimalarial therapeutic strategy.

PIEZO1 as Carrier Molecule for Er Antigens Blood Group

Alloimmunization refers to an immune response to foreign antigens from another human. The presence of alloantibodies may have clinical consequences for pregnant women, potentially resulting in hemolytic disease of the fetus and newborn, and for people who need a transfusion by triggering an attack by the immune system. We are all familiar with the 2 main blood group systems, namely the ABO and the Rh systems. However, there are many more blood group systems (45 recognized) containing 360 red cell antigens. In a recent study, Karamatic Crew et al[148] investigated individuals with alloantibodies against a collection of antigens termed Er that were first observed more than 40 years ago[149] but were yet to be genetically characterized. Using whole-exome and sanger sequencing of these individuals, they identified specific changes in the gene coding for *PIEZO1*, resulting in the production of an altered protein at the cell surface. Using in vitro approaches, they conclusively demonstrate that alloantibodies to Er (including 2 never reported) bind to PIEZO1 and that PIEZO1 is required for Er antigen production. Thus, and despite its relatively low abundance in RBC membranes,[122] PIEZO1 was shown to be the genetic carrier of the Er blood group system.[148] The discovery of the genetic basis of the Er blood group should allow to develop new tests to identify individuals with this rare blood group, with the aim of providing better care to patients.

PIEZO1 Contributes to Platelet Aggregation

Mechanical forces play a critical role in platelet activation involved in clot formation in hemostasis and pathological thrombus formation.[150,151] PIEZO1 expression in platelets, as well as in a megakaryoblastic cell line, leads to shear stress–induced Ca^{2+} signal.[152] Shear stress activation of platelet PIEZO1 contributes to collagen-induced platelet aggregation and thrombus formation

in vitro.[152,153] Importantly, Zainal Abidin et al[154] show that PIEZO1 initiates the platelet response to supraphysiological free-flow acceleration, a mechanism occurring in circulating platelets before platelet adhesion to subendothelial matrix exposure or artificial device surfaces. This response to extensional strain generated by flow acceleration primes platelets for immediate downstream aggregation. Activation of platelets by free-flow acceleration is mediated by Ca^{2+} transients. These Ca^{2+} signals result from the sequential activation of PIEZO1, which senses membrane deformation and triggers downstream ATP release from PANX1 (pannexin 1), leading to autocrine activation of P2X1 (purinoceptor P2 type 1) channels (Figure 6).[154] Therefore, PIEZO1 involvement in initial steps of platelet activation is of direct clinical relevance for pathological thrombosis in stenosed vessels.

PIEZO1 Contributes to Immune Cell Functions

Immune cells are exposed to various mechanical forces during their lifetime, from circulation in the lymphatic and blood systems to their trafficking in organs with various tissue stiffness. PIEZO1 has been shown to sense pressure and shear stress in myeloid cells recruited to the lung, heart, and tumors, where its activity stimulates inflammation.[155–157] Substrate stiffness–dependent modulation of PIEZO1 activity modulates cytokine-induced activation of macrophages in vitro.[158] Consistently, PIEZO1 modulates the macrophage activation in response to stiff material implants in vivo.[158] In dendritic cells, PIEZO1 also contributes to mechanical stiffness sensing supporting optimal metabolism and function.[159,160]

Pharmacological or shear stress activation of PIEZO1 in vitro also contributes to optimal activation of T cells.[161,162] However, Jairaman et al[163] have shown that deletion of PIEZO1 in T cells does not impact effector $CD4^+$ T-cell response in experimental autoimmune encephalomyelitis, an in vivo murine model of multiple sclerosis, although it attenuates disease severity. The PIEZO1 deletion beneficial effect on disease severity is instead mediated by selectively enhancing regulatory T-cell expansion, increasing the potential of regulatory T cells to mitigate autoimmune neuroinflammation.[163]

In line with its function in immune cells, a PIEZO1 GOF mutation associated with iron overload in mouse has been shown to increase macrophage phagocytic activity. Macrophages with overactive PIEZO1 enhance erythropoiesis, increasing the production of erythroferrone that in turn downregulates hepcidin expression in hepatocytes, a hormone involved in the regulation of iron metabolism. This mechanism could contribute to the higher serum iron levels in humans with PIEZO1 GOF mutations.[164]

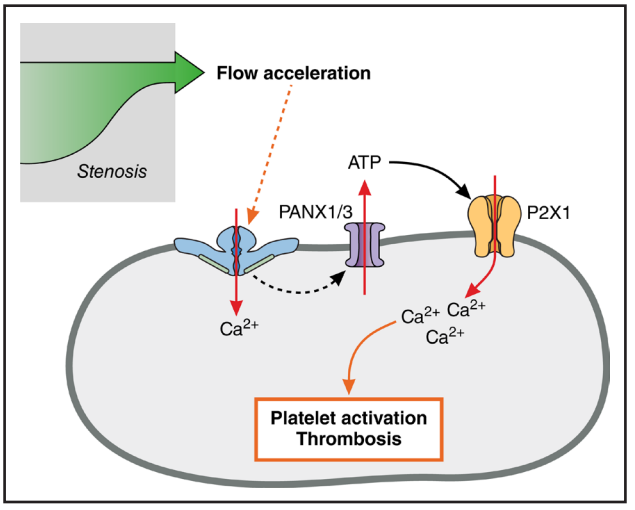

Figure 6. PIEZO1 contribution to platelet activation.
Extensional strain generated on circulating platelets by acceleration of blood flow, such as may occur during stenosis, leads to sequential activation of PIEZO1, PANX1 (pannexin 1), and P2X1 (purinoceptor P2 type 1) receptors. Ca^{2+} entry resulting from PIEZO1 activation, and subsequent P2X1 receptor stimulation induces platelet priming for downstream aggregation. This makes PIEZO1 pathways attractive targets in certain hemorrhagic or thrombotic disorders. Illustration credit: Sceyence Studios.

ROLE OF PIEZOS IN SINO-AORTIC MECHANOSENSORY RECEPTORS

PIEZO1 and PIEZO2 Channels as Sensors of BP

The baroreflex serves to adjust heart activity to BP fluctuations. Distinct populations of stretch-sensitive myelinated vagal afferents (baroreceptors), are found in the heart and adjoining coronary and pulmonary circulations. BP pulses that occur with each heartbeat radially stretch the elastic vessel wall, which in turn activates the mechanosensory endings. Afferent neuronal signals are then transmitted to the central nervous system and inform about stretch magnitude, pulse frequency, and mean arterial pressure. Parallel central pathways are engaged that decrease sympathetic output and enhance parasympathetic output, ultimately decreasing heart rate, cardiac output, and vascular resistance (Figure 7).[165,166] Altered baroreceptor function and sensitivity predict arrhythmias and premature death in humans after myocardial infarction or heart failure (Figure 7).[167]

The physiological regulation of arterial BP by baroreceptors located in the ascending aorta and carotid sinuses is relatively well understood; however, the molecular sensors that detect change in BP remained unknown until recently. Recent studies in mice provided evidence for a contribution of both PIEZO1 and PIEZO2 as transducers of BP (Figure 7).[48] Conditional disruption of either PIEZO1 or PIEZO2 had no effect on BP or baroreceptor reflex, but combined genetic ablation of both genes in nodose (jugular) and

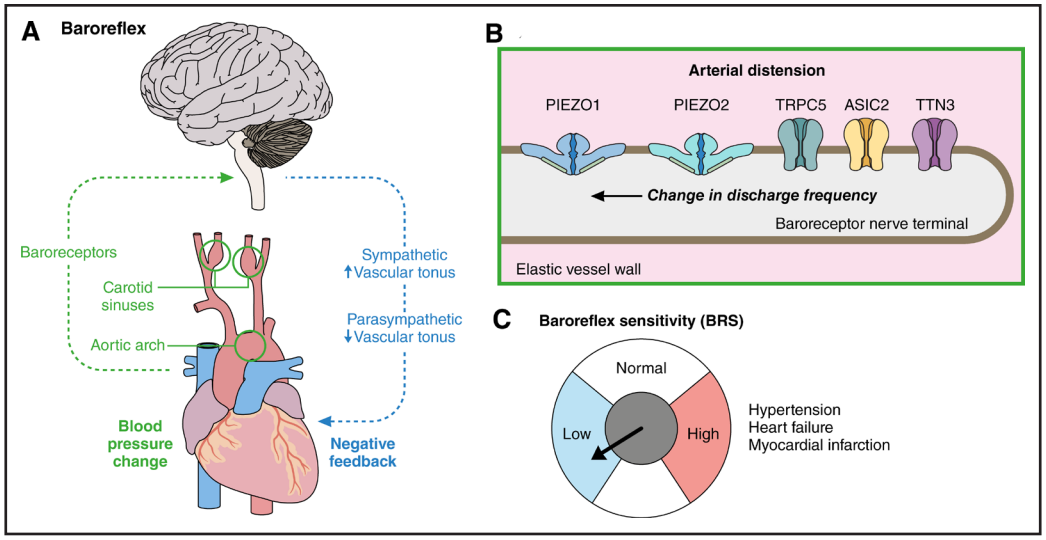

Figure 7. PIEZOs as sensors of blood pressure.

A, Schematic representation of the baroreflex. Baroreceptors (BRs) are mechanosensitive nerve endings in carotid sinuses and aortic arch that exert control of mean arterial pressure. The vagus nerve and the glossopharyngeal nerve are 2 afferent nerves that innervate the aortic arch and carotid sinus. Baroreceptor activation generates afferent nerve impulses that are conveyed to the cardiovascular center in the pons and medulla. Stretching of the baroreceptors because of increased blood pressure causes an increase in the activity of the vagal nerve and concomitantly inhibits the sympathetic outflow, ultimately leading to decreased heart rate and blood pressure. Conversely, decreased blood pressure results in decreased signal output from the BRs, leading to decreased parasympathetic activity and disinhibition of the central sympathetic control regions. **B**, The stretch sensory nerve endings of BRs encompass a few mechanosensitive channels that can potentially respond to vascular distension (mechanoelectrical transduction). Subsequent excitation of the afferent fibers is relayed to the nucleus tractus solitarius, the primary visceral sensory relay station within the brain. **C**, The alteration in the sensitivity of the baroreceptor–heart rate reflex (baroreflex sensitivity, BRS) contributes to sympathetic–parasympathetic imbalance and is known to predict the risk of cardiovascular events. Decrease in BRS (arrow) is associated with myocardial infarction, heart failure, and hypertension. ASIC2 indicates acid-sensing ion channel 2; TRPC5, TRP channel classical subtype 5; and TTN3, tentonin 3. Illustration credit: Sceyence Studios.

petrosal (glossopharyngeal) sensory ganglia abolished reflex decrease in heart rate and aortic depressor nerve responses induced by vasoconstriction.[48] Double KO mice also display labile hypertension and increased BP variability.[48] In addition, Cre-guided ablation of nodose and petrosal ganglion PIEZO2 neurons eliminates the baroreceptor reflex and the aortic depressor nerve effects on BP and heart rate.[168] Interestingly, genetic mapping reveals that PIEZO2 neurons have unique mechanosensory terminals, forming end-net endings surrounding the aortic claws, a macroscopic structure probably suited to detect arterial wall distension.[168] Together, these data suggest that both PIEZO1 and PIEZO2 are essential for baroreceptor function and may collaborate in the same class of sensory neurons to sense arterial stretch. However, significant concerns regarding the evidence supporting the role of PIEZOs in barosensation have been raised.[169] For example, the fact that inactivation of PIEZO2 gene alone had no effect when PIEZO1 is preserved,[169] suggests that at least some PIEZO2 neurons depend on PIEZO1 for their function. However, *PIEZO1* mRNA was rarely colocalized with *PIEZO2* in nodose and petrosal ganglion neurons.[169] Therefore, the exact role of PIEZO1 and the extent of interaction between PIEZO1 and PIEZO2 in baroreceptors remain unclear. Recent data also show that PIEZO2, but not PIEZO1, acts as barosensor to regulate arterial BP in Wistar-Kyoto rats.[170] The expression of PIEZO2 was significantly downregulated in nodose ganglion neurons and aortic nerve endings in spontaneously hypertensive rats and different inducible models.[170] Coimmunoprecipitation experiments suggested that PIEZO2 activity was downregulated by the Nedd4-2 (neural precursor cell–expressed developmentally downregulated gene 4 type 2) in baroreceptor nodose neurons, causing hypertension in rats. These findings reinforce the role of PIEZO2 in baroreceptor function and its critical role in the pathogenesis of hypertension.

Besides PIEZO1 and PIEZO2, other ion channels have been proposed to contribute to the baroreflex mechanotransduction; these include the γENaC (epithelial sodium channel γ subunit),[171] ASIC2 (acid-sensing ion channel 2),[172] and the TRPC5 (TRP channel classical subtype 5).[173] However, substantial residual baroreflex is still observed although these channels are eliminated or blocked. More recently, the cation channel TTN3 (tentonin 3/TMEM150C), was shown to be expressed at the vagus afferent nerve endings innervating the aortic arch to function as a baroreceptor.[174] Genetic ablation of TTN3 induced ambient hypertension, tachycardia, and impaired baroreflex sensitivity. However, the function of TTN3 is still debated because, as for the above-cited candidate channels, it does not exhibit all the features that define a genuine mechanosensitive ion channel.[4]

Overall, these studies expand the molecular profiles of baroreceptors and provide new insights into molecular mechanisms regulating cardiovascular functions through baroreceptor function. Attenuated baroreflex sensitivity is attributed to cardiac arrhythmogenesis during heart failure. Therefore, targeting PIEZO proteins, and other sensors, pharmacologically might represent a novel strategy for activating baroreceptors and treating hypertension.

GENETIC LINKAGE TO HUMAN CARDIOVASCULAR DISEASES

The reported mutations of *PIEZO* genes in human diseases underline the importance of PIEZO1 in cardiovascular functions (Table). No cardiovascular-related clinical condition has been reported so far for patients carrying a PIEZO2 mutation. Of note, *PIEZO* mutations give rise to diseases with highly variable clinical expression, illustrated by the phenotypes of patients with DHS ranging from asymptomatic to severe with massive hemolysis. The variable expressivity of the clinical conditions could be explained by epigenetic factors or by the combination of PIEZO mutations with polymorphic variants or other disease-causing alleles.[175]

DHS-inducing mutations that have been functionally characterized are mostly missense mutations leading to slight or moderate slowing of channel inactivation kinetics and subsequent increased signaling for a given stimulus.[127,129] However, mutations associated with generalized lymphatic dysplasia or bicuspid valve formation lead to attenuated or abolished PIEZO1 activity. These mutations lead to either truncated channels or channels from mis-spliced mRNA or to channels that display decreased mechanical sensitivity or reduced plasma membrane trafficking due to altered N-glycosylation status.[84,126,184] Accordingly, DHS- and LGD-linked mutations are classified into GOF and loss-of-function mutations, respectively. Interestingly, GOF and loss-of-function mutations can lead to overlapping phenotypes, such as fetal hydrops, perinatal edema, and lymphedema in adults for PIEZO1 or arthrogryposis for PIEZO2 (Table). The similar clinical features induced by *PIEZO1* mutations having opposite effects on channel functions reflect the prominent role of PIEZO1 in vascular homeostasis. Therefore, any imbalance in PIEZO1 activity and signaling could lead to overlapping phenotypes.

Some pathologies may arise not specifically from mutations in the channel but from altered gene expression. In addition to gene variants linked to diseases, increase in PIEZO1 expression has been associated with cardiovascular diseases in humans. PIEZO1 was found to be upregulated in myofibroblasts in the fibrous cap of the plaque in patients with symptomatic carotid atherosclerotic plaques.[185] PIEZO1 was also upregulated in arterial smooth muscle cells in patients with idiopathic pulmonary hypertension.[76,186,187] It remains to be established whether alteration in PIEZO1 expression is the cause or consequence of the cardiovascular diseases.

PIEZO CHANNELS AS THERAPEUTIC TARGETS?

Compelling evidence points to the importance of PIEZO channels in many aspects of cardiovascular health and disease. Better understanding of PIEZO protein biology

Table. Association of PIEZO Mutations With Human Diseases

Gene	Impact on channel activity	Clinical conditions	Reported cardiovascular-related clinical features	Selected references
PIEZO1	Gain-of-function	Autosomal dominant dehydrated hereditary stomatocytosis (OMIM 194380)	RBC dehydration	127–132,144,164,176,177
			Hemolytic anemia	
			Pseudo-hyperkalemia	
			Haemochromatosis (increased plasma iron)	
			Fetal hydrops/perinatal edema	
			Lower limb lymphedema in adult	
	Loss-of-function	Autosomal recessive generalized lymphatic dysplasia of Fotiou (OMIM 616843)	Asymptomatic occasional spherocytes and stomatocytes	84,85,126
			Fetal hydrops/perinatal edema	
			Lymphangiectasia	
			Mild overhydration of RBCs	
		Dominant bicuspid aortic valve disease	Mild-to-moderate aortic regurgitation	63
PIEZO2	Gain-of-function	Gordon syndrome (OMIM 114300)		178,179
		Distal arthrogryposis type 5 (OMIM 108145) Marden-Walker syndrome (OMIM 248700)		
	Loss-of-function	Arthrogryposis, distal, with impaired proprioception and touch (OMIM 617146)		180–183

RBC indicates red blood cell.

therefore may lead to new treatments in the near future. However, this research field faces several limitations and technical obstacles. First, there is a limited number of agonists and antagonists. Except for the small-molecule, gating modifier Yoda1[18,35] that serves as valuable tool compound both in vitro and in vivo, PIEZO2 agonists and specific PIEZO1/2 antagonists have yet to be identified. Yoda1 also has its own limitations for its use in vivo, due to its relatively low affinity for PIEZO1 and low water solubility. Nevertheless, the unique protein structure of PIEZO proteins should make possible to develop more specific pharmacological agents and to discover PIEZO antagonists. A key objective therefore of high-throughput screening and computational methods for effective ligand screening is to develop high-quality pharmacological tools for the development and validation of PIEZO drugs. On a positive note, homozygous *PIEZO1* disruption in humans is not lethal, suggesting that adverse drug reactions may be limited in PIEZO1-drug medication. Even with lead compounds in hands drugs often fail in later stages of development due to safety and efficacy concerns. Given the broad biological expression of PIEZOs in various tissues and cell types, a challenge will be to achieve desirable therapeutic effects while limiting unwanted effects. For example, the use of PIEZO1 as a pharmacological target in atherosclerosis and hypertension is promising but is clearly hampered by its expression in RBCs and immune cells, which could lead to serious adverse effects.[155] As for PIEZO2, its involvement in various somatosensory functions may also make it difficult to achieve efficient inhibition of mechanical allodynia, the most common symptom associated with neuropathic pain while avoiding interfering with BP regulation and respiration. Off-target effects of systemically administered PIEZO drugs will be a major hurdle in designing therapies with desired efficacy and acceptable toxicity. Developing targeting strategies to enable site-specific PIEZO drug delivery will be necessary to reduce off-target effects and enhance therapeutic efficacy. For example, peptide- and antibody-based targeting strategies are currently used in oncotherapy to deliver drugs to tumor cells or tissues.[188] Synthesizing antibody-drug conjugates consist of the antibody, which targets an antigen exposed at the cell surface, chemically linked to the active therapeutic agent, known as the warhead. However, this approach is currently limited to highly potent drugs, given the large size of antibodies that gives a low loading efficiency. Other alternative nanocarrier-based targeted drug delivery strategies (aptamers, small molecules, etc.) and delivery vehicles (liposomes, polymers, metal oxides, etc.) may be better suited to achieve site-specific drug delivery and thereby enhancing the drug's therapeutic efficacy.[189] To sum up, mouse and human data outlined above suggest that PIEZO protein targeting has the potential to produce significant therapeutic effects. However, there is still a long way to go before PIEZO proteins can be validated as drug targets for cardiovascular diseases.

CONCLUSION AND PERSPECTIVE

The cardiovascular system is continuously exposed to hemodynamic forces.[9] Cardiomyocytes are stretched as the heart fills with blood, vascular ECs experience shear stress, circumferential stress, and axial stress while baroreceptive nerve endings respond to vascular distension. Hemodynamic factors influence all forms of vascular growth, including angiogenesis, vasculogenesis, and arteriogenesis. Sustained elevation of BP elicits a host of mechanobiological responses by arteries that often induce phenotypic changes in the primary cells, associated with tissue remodeling. Thus, uncovering the mechanisms of cardiovascular mechanotransduction is important for understanding both the maintenance of physiology and the development of disease, as well as for providing therapeutic targets and strategies for treating cardiovascular pathologies.

Compelling evidence demonstrates the role of PIEZO channels, especially PIEZO1, in cardiovascular mechanotransduction. Cardiovascular relevance of PIEZO1 channels initially rose from studies investigating endothelial responses to shear stress,[27,29] but widespread expression and multiple roles are now increasingly appreciated. PIEZO1 is activated by hemodynamic forces that influence vessel size and morphology and promote vasoactive responses. By virtue of its expression in RBCs and immune cells, PIEZO1 contributes to RBC volume regulation and immune surveillance. PIEZO2 has been proposed to contribute to the baroreflex mechanotransduction. Dysfunction or dysregulation of PIEZO1 is associated with various cardiovascular defects including hemolytic anemia, lymphedema, pulmonary hypertension, atherosclerosis, thrombus formation, and ventricular hypertrophy. Thus, tremendous information has been gained from animal models and clinical studies, providing important insight into the mechanobiological PIEZO mechanisms that control cardiovascular functions and diseases.

The ability of PIEZO channels to regulate many cellular functions lies in its capacity to activate numerous signaling pathways and to interact with many structural elements of the cytoskeleton and the plasma membrane. PIEZO channel opening leads to Ca^{2+} entry into the cell, which activates intracellular Ca^{2+} signaling pathways and regulates cellular functions depending on the cell type. In addition, PIEZO protein regulates the formation of actin-based stress fibers and has dynamic interaction with the cytoskeleton and the integrins. Some preferential coupling however is found in different cell types. PIEZO1 coupling to pannexin and ATP release has been reported in many cell types, including ECs to enhance NO production,[71] lung alveolar epithelial type I cells to promote surfactant secretion,[190] odontoblasts to

participate in dentinal sensitivity,[191] and cholangiocytes to contribute to bile secretion.[192] Likewise, the PIEZO1-YAP axis has recently emerged as an important pathway common to different cell types including cardiovascular cells. The YAP and TAZ (transcriptional coactivator with PDZ-binding motif) transcription factors read and translate a broad range of mechanical cues into cell-specific transcriptional programs.[193] The PIEZO1-YAP axis has a key role in cancer metastasis,[194,195] neuronal specification in human neural stem cells,[196] and bone homeostasis in osteoblastic cells.[197] In aortic valve, interstitial cells the PIEZO1-YAP axis promotes osteogenic differentiation that contributes to calcific aortic valve disease[198] and mediates the endothelial atherogenic inflammatory response in ECs.[199] Thus, the PIEZO1-YAP axis emerges as an important pathway that may contribute to cell remodeling in cardiovascular diseases.

Nevertheless, various questions need to be addressed for a better understanding of the function of PIEZO channels in cardiac functions and for improving the treatment of cardiac diseases. What is the precise subcellular localization of functional PIEZO channels in cardiovascular cells and what molecular determinants are responsible for their subcellular localization?[61,123] Development of more specific antibodies, in addition to genetically engineered mouse models, are important requirements for these histochemical studies. How do PIEZO channels discriminate local mechanical information over bulk tension? What are the specific signaling pathways mobilized by PIEZO channel-induced calcium influx in the different cardiovascular cells? How does abnormal activation of PIEZOs mobilize pathogenic pathways in disease? Is there an interaction or compensation action between PIEZO1 and PIEZO2 in barosensation? Can the control of PIEZO2 activity in baroreceptors be considered a therapeutic strategy to regulate hypertension? Given the broad expression and biological roles of PIEZO1 in the various cardiovascular cell types, how should PIEZO1 be specifically targeted to treat cardiovascular diseases? Current drugs are restricted to activators with poor solubility or low affinity, and to blockers with poor selectivity. Therefore, it will be helpful to identify specific activators and inhibitors of PIEZOs based on their structure, both for studying their pathophysiological role and for investigating therapeutic strategies. When targeting PIEZO1 may be used as a treatment strategy, understanding how tissue- and cell-specific factors regulate its mechanical sensitivity and gating will improve the potency of any potential treatment. Therefore, PIEZO drugs with tissue specificity, and drugs targeting PIEZO signaling pathways may provide an alternative approach for future disease treatments. Answering all these questions will provide deep understanding of cardiovascular physiology and pathology and will make PIEZO channels a novel target for treating a wide range of cardiovascular diseases.

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Disclosures

None.

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