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# Piezo channels

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## ***What are Piezo proteins?***

Piezo proteins constitute the first family of excitatory ion channels gated by mechanical forces described in vertebrates. These ion channels are involved in cell mechanotransduction, the conversion of mechanical forces into biological signals.

## ***Is mechanotransduction important?***

Yes it is! All living organisms are subjected to mechanical forces from their environment and rely on mechanotransduction for their survival. For instance, our senses of touch, mechanical pain, proprioception, hearing and balance depend on mechanically-activated channels. And besides sensory systems, mechanotransduction is involved in diverse physiological functions including vascular tone and blood flow regulation, bone and muscle homeostasis, flow sensing in kidney and respiratory systems.

## ***Does mechanotransduction rely exclusively on mechanosensitive channels?***

No, it does not. Cells integrate a variety of mechanical stimuli such as shear stress, tension, torsion and compression and translate them into short term effects (i.e. changes in ion concentrations and voltage) and long term effects via changes in gene expression. Many membrane-associated molecules are involved in mechanotransduction including ion channels, specialized cytoskeletal proteins, cell junction molecules, G-protein-coupled receptors and kinases. The specificity of mechanosensitive ion channels is to convert mechanical forces into electrical signal within tens of microseconds. This is particularly suited for fast signaling that occurs into specialized sensory cells involved in touch and hearing.

## ***So, why is Piezo discovery valuable for mammalian physiology?***

Although some mechanically-activated ion channels have been characterized decades ago in bacteria and invertebrate species, these channels are either not conserved in vertebrates or have lost their mechanotransduction properties during evolution towards higher species. Therefore, the molecular identification of mammalian mechanotransduction channels has remained a long-standing question in the field of sensory functions. The discovery of Piezo proteins in 2010 has fueled mechanotransduction-related research, opening the field for prolific work in a wide range of research area over the past few years.

## ***What is known about Piezo genes?***

There is no *piezo* gene in bacteria, but *Piezo* homologues are found in plants and animals including protozoa. Most vertebrates have two copies of *Piezo* genes, *Piezo1* and 2, encoding relatively large proteins of over 2 500 and 2 800 amino acids in human, respectively. These genes are expressed in a wide range of tissues in mammals, highlighting potential contribution of Piezo channels to mechanotransduction in various organs.

### ***What does Piezo channel look like and how does it sense force?***

Piezo1 assembles as a 900 kDa homo-trimeric complex to form an ion channel with a propeller-like structure surrounding a central pore module. Residues forming the ion conducting pathway of this pore module are encompassed in the C-terminus quarter of the Piezo subunit. Piezo channels are functional in artificial membrane demonstrating that the channel can detect changes in membrane tension in the absence of other cellular components, but the structures of the force sensor(s) and transducer element(s) that gates the ionic pore remain to be determined.

### ***What kind of stimulation leads to Piezo activation?***

Piezo channels can be activated by many mechanical stimuli *in vitro*. If some of these stimulations directly mimic physiological forces experienced by cells *in vivo*, such as shear-stress applied in a microfluidic chamber, the most commonly used methods consist of stretching the membrane by applying positive or negative pressure through a patch-clamp recording electrode or by poking the membrane using a blunt glass pipette. The main limitation of these techniques is that the amount of force required to gate Piezo channels cannot be accurately determined. Therefore, efforts are made to develop other methods such as stimulation with atomic force microscopy cantilever to precisely quantify the force applied or the use of magnetic nanoparticles linked to the channel to apply much localized pulling forces. Despite still limited pharmacology, screening over 3 million compounds identified Yoda1, a synthetic small molecule leading to Piezo1 activation by lowering its mechanical sensitivity.

### ***What type of ionic current is mediated by Piezo channels?***

Activation of Piezo channels generates cationic non-selective currents, *i.e.* these channels are permeant to monovalent cations such as Na<sup>+</sup> and K<sup>+</sup> and to divalent cations such as Ca<sup>2+</sup> and Mg<sup>2+</sup>. Therefore, Piezo are excitatory channels, their activation producing membrane depolarization, and channel openings lead to Ca<sup>2+</sup> entry in the cell potentially triggering intracellular calcium signaling pathways (Figure 1). Piezo currents inactivate during prolonged stimulations with relatively fast inactivation kinetics at negative potential (on a millisecond time-scale) that tend to become slower as membrane potential increases.

### ***Are Piezo channels involved in mechanosensation?***

Yes they are! Piezo2 is expressed in a subset of somatosensory neurons, the receptor cells that project in the whole body and are involved in the detection of touch, pain and proprioception. Since *Piezo2* constitutive knock-out (KO) induces perinatal lethality, the physiological role of Piezo2 in mechanosensation has been characterized using conditional KO in sensory neurons. These studies demonstrated a crucial role of Piezo2 in light touch sensing as well as in proprioception, while ruling out its involvement in mechanical pain. Moreover, Piezo2 expressed in vagal and spinal sensory neurons innervating the respiratory system contributes to airway stretch sensing and mediates lung inflation-induced apnoea. Therefore, respiratory defects are likely the cause of constitutive *Piezo2* knock-out lethality.

### ***... And in hearing?***

Auditory hair cells contain mechanosensitive channels in their stereocilia that detect sound-induced vibrations. A recent study has shown that Piezo2 is expressed in hair cells. However, Piezo2 is localized in the apical membrane of hair cells, is responsible for a reverse-polarity current but not for the sensory-transduction current, and its specific deletion in these cells only induces a mild auditory defect in mice. These results highlight the presence of at least two molecularly distinct mechanosensitive channels in auditory hair cells among which Piezo2 is not the “hearing” channel. Precise function of Piezo2 in hair cells requires further characterization.

### ***What about Piezo1?***

Although Piezo1 has not been implicated so far in neuro-sensory functions, several studies identified Piezo1 as a sensor of mechanical forces in endothelial, urothelial and renal epithelial cells. In particular, Piezo1 is involved in shear-stress sensing in blood vessel endothelial cells and is implicated in developmental and physiological functions of the circulatory system, including proper formation of blood vessels, regulation of vascular tone and remodeling of small resistant arteries upon hypertension. The crucial role of Piezo1 in circulatory system development causes embryonic lethality of *Piezo1* KO mice.

In addition to its role in setting up and maintaining blood vessel integrity, Piezo1 is involved in red blood cells (RBC) volume homeostasis. Erythrocytes experience significant mechanical forces while circulating, and mechanosensitive Piezo1 channels act upstream of a calcium activated potassium channel, KCNN4 (also called Gardos channel), which regulates intracellular cationic content and cell volume. Consequently, *Piezo1* deletion in mice leads to overhydrated RBCs.

### ***Are there human diseases associated with PIEZO1 mutations?***

Yes, *PIEZO1* mutations have been linked to two main types of human disorders. Several autosomal dominant mutations, among which some were characterized *in vitro* and lead to increased *PIEZO1* signaling, are associated with dehydrated hereditary stomatocytosis (DHS). DHS is characterized by RBC osmotically driven dehydration that can lead to haemolytic anaemia. Therefore *Piezo1* deletion in mice leads to overhydrated RBCs whereas “gain of function” mutations in human lead to dehydrated RBCs, highlighting its crucial role in volume homeostasis.

Other *PIEZO1* mutations resulting in attenuated or disrupted *PIEZO1* function have been linked to autosomal recessive generalized lymphatic dysplasia, a congenital disease that lead to persistent lymphoedema, enlightening the involvement of *PIEZO1* in the development of lymphatic structure. Piezo1 is a widely-expressed ion channel and the full extent to which it regulates development and physiology is yet to be elucidated.

### ***... And with PIEZO2 mutations?***

Autosomal dominant *PIEZO2* mutations thought to cause “gain of function” effect have been linked to different forms of distal arthrogryposis and to Marden-walker syndrome. These conditions are multi-symptomatic human disorders presenting overlapping phenotypic characteristics, including short stature, curved fingers with straight thumbs and contractures of hands and feet. The broad spectrum of clinical defects associated with these diseases suggests *PIEZO2* involvement in development and function of various structures in the body. Furthermore, several cases of recessive mutations

leading to truncated proteins or malfunctioning channels have been reported. These patients display a progressive phenotype mostly distinct from dominant mutations despite partial overlap such as short stature and contractures. In addition to scoliosis, myopathy and progressive respiratory failure, disruption of PIEZO2 function leads to proprioception and discriminative touch perception impairments, accordingly to Piezo2 critical role in mice in light-touch sensing and proprioception.

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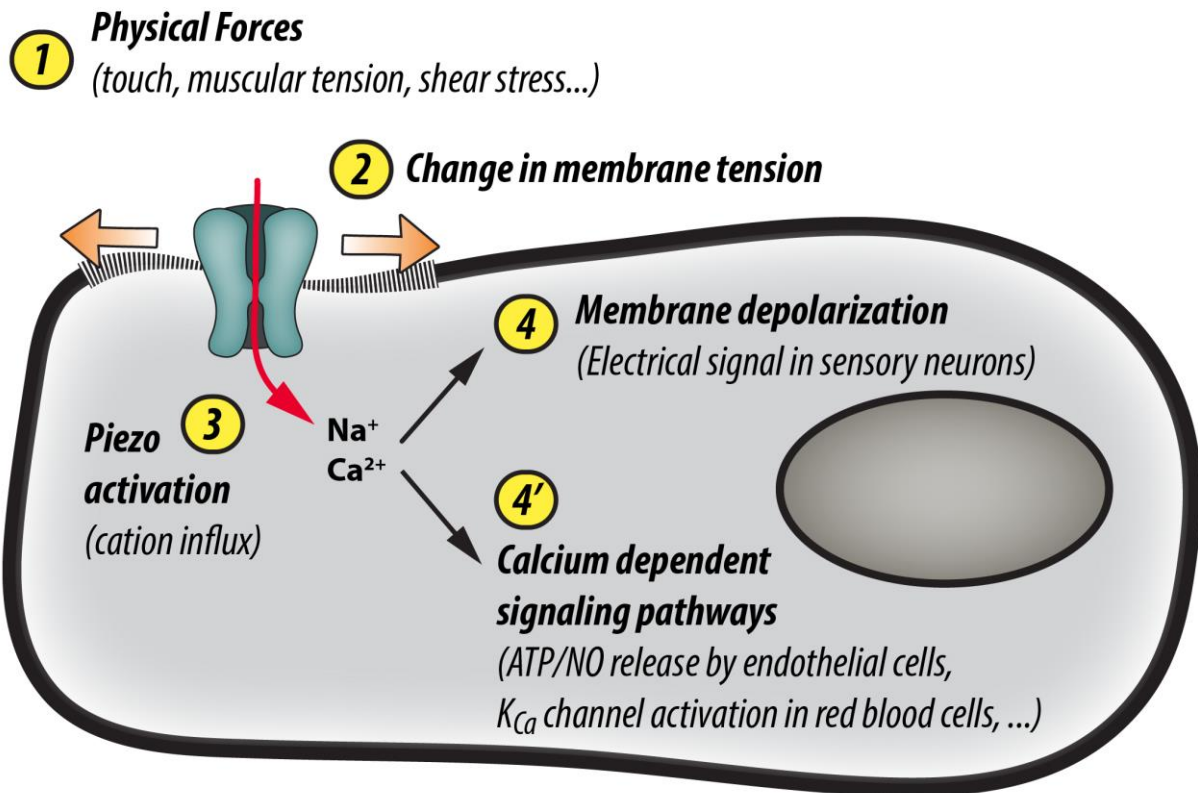


Figure 1. Piezo-dependent mechanotransduction.  
Various mechanical stimuli exerted on cells induce changes in plasma membrane tension, eliciting Piezo channel openings. Resulting cation influx can trigger sensory neuron firing or activation of intracellular calcium signaling pathways.