Structure and mechanogating mechanism of the mechanosensitive Piezo channel

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The mechanosensitive Piezo channels function as key eukaryotic mechanotransducers. However, their structures and mechanogating mechanisms remain unknown. Taking a multidisciplinary approach combining protein engineering and purification, cryo-EM, high-throughput drug screening, mutagenesis and electrophysiology, we have first determined the three-bladed, propeller-shaped structure of mouse Piezo1, and then functionally identified the bona-fide ion-conducting pore, key pore-property-determining residues, and mechanotransduction components. Despite the lack of sequence repetition, we identify nine repetitive units consisting of four transmembrane helices (TM) each-which we term transmembrane helical units (THUs)-which assemble into a highly curved blade-like structure. The last TM encloses a hydrophobic pore, followed by three intracellular fenestration sites and side portals that contain pore-property-determining residues. The central region forms a 90 Å-long intracellular beam-like structure, which undergoes a lever-like motion to connect THUs to the pore via the interfaces of the C-terminal domain, the anchor-resembling domain and the outer helix. Deleting the extracellular loops connecting TM15-16 and TM19-20 in the distal THUs or mutating leucine residues at 1342 and 1345 in the beam impairs the mechanical activation of Piezo1. Furthermore, we have identified a novel set of Piezo1 chemical activators, termed Jedi, which activates Piezo1 through the extracellular side of the blade instead of the C-terminal extracellular domain of the pore, indicating long-range allosteric gating. Remarkably, Jedi-induced activation of Piezo1 requires the key mechanotransduction components, including the two extracellular loops in the distal THUs and the two leucine residues in the proximal end of the beam. Overall, Piezo1 possesses a unique 38-TM topology and employs the peripheral blade-beam-constituted lever-like apparatus as a designated transduction pathway for long-distance mechano- and chemical-gating of the central pore (Nature 2015, 2018; Neuron 2016; Nat Communs 2017, 2018).