The molecular mechanisms of the mechanosensitive Piezo1 ion channel

Supported by the National Natural Science Foundation of China and the Ministry of Science and Technology of China, the research group led by Prof. Xiao Bailong (肖百龙) at the School of Pharmaceutical Sciences, Tsinghua-Peking Joint Center for Life Sciences, and IDG/McGovern Institute for Brain Research, Tsinghua University, published a research article entitled "Ion Permeation and Mechanotransduction Mechanisms of Mechanosensitive Piezo Channels" in *Neuron* (2016, 89(6): 1248—63), providing important insights into the ion-conducting and mechanotransduction mechanisms of an evolutionarily conserved and physiologically important class of ion channels.

Mechanosensitive channels represent a class of ion channels that respond to mechanical force stimulation and allow ions to enter or exit cells. They have been proposed to serve as key mechanotransducers for mechanotransduction, but the molecular identities of mechanosensitive cation channels in mammals were unknown until the identification of the evolutionarily conserved Piezo family of proteins including Piezo1 and Piezo2 in 2010. Since then, the roles of Piezo proteins in various physiological processes and human diseases have been demonstrated. Piezo1, for example, plays a key role in sensing blood-flow-associated shear stress and, consequently, controlling vascular development and function. By contrast, Piezo2 mediates gentle touch sensation and proprioception. In humans, mutations of Piezo1 or Piezo2 genes have been linked to various genetic diseases. These findings demonstrate the functional importance of Piezo channels, as well as their pathological relevance and potential as therapeutic targets.

However, important fundamental questions regarding how this prototypic class of mechanosensitive functions at the molecular level remain unsolved, among which are how these proteins three-dimensionally organize into mechanosensitive channels, and how they conduct ions and respond to force stimulation.

After setting up his own lab in Tsinghua University, Dr. Xiao has focused on tackling these questions. In a paper published in *Nature* in 2015, they, along with collaborators, first reported the cryo-electron microscopy (cryo-EM) structure of the full-length mouse Piezo1 at a resolution of 4.8 Å. The overall architecture of Piezo1 was organized into a unique three-bladed, propeller-shaped structure and the peripheral modules might function as force sensors and transducers to gate the central pore (Fig A). However, due to the limited resolution, the primary sequence that underlies the distinct structure domains of the Piezo1 structure remains elusive. For example, it was not clear whether the ion-conducing pore is located. In the paper published in *Neuron*, Xiao and colleagues have for the first time functionally unveiled the bona fide pore module (residues 2,189—2,547) of mPiezo1 that crucially governs the fundamental pore properties and the mechanotransduction module (residues 1—2,190) that is sufficient to confer mechanosensitivity to trimeric channel pores such as Piezo1 channels and Acid Sensing Ion channel 1 (ASIC1) (Fig B, C). This study has thus revealed the basic principles that enable Piezo proteins to function as sophisticated mechanosensitive cation channels.

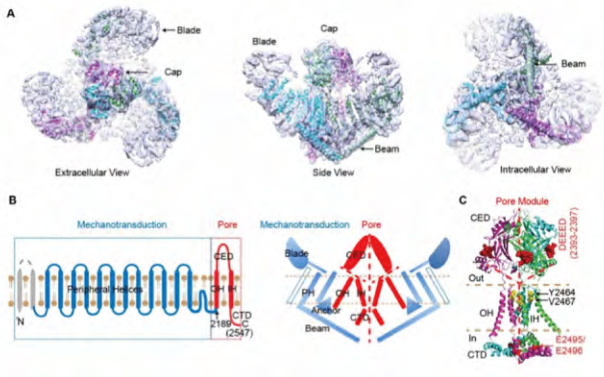

Figure The architecture and molecular mechanisms of mechanosensitive Piezo1 cation channel.