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Structural Biology: Piezo Senses Tension through Curvature

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Abstract

The sensations of sound, touch and pressure are mediated by mechanotransduction channels — transmembrane proteins whose ionic permeabilities are gated by mechanical forces. New structures of Piezo1 by cryoEM lead to the suggestion that this channel might sense membrane tension through changes in the local curvature of the membrane.

Mechanotransduction is the process by which cells convert mechanical stimuli, such as sound, accelerations, touch and pressure, into changes in electrochemical activities, such as transmembrane voltage or calcium concentration. Mechanotransduction is mediated by force-sensitive ion channels, transmembrane proteins whose ionic permeabilities are gated by mechanical forces acting directly on them [1]. Earlier structural and functional studies have elucidated two gating mechanisms: mechanical forces acting either via the cytoskeleton [2,3] or through tension in the membrane [4]. Structural studies using cryoEM of mouse Piezo1 (mPiezo1) [5–7], a member of a newly discovered family of channels [8], lead to the suggestion of a third gating mechanism: channel opening in response to change in the local curvature of the membrane [5].

How are channels gated by force? Not long ago, the atomic structure of NompC, a eukaryotic force-sensitive TRP ion channel in invertebrates and lower vertebrates, revealed a tetrameric bundle of helices formed by four 29-ankyrin-repeat domains, one in each subunit [2]. The bundle is thought to act as a spring that transmits force from the microtubule cytoskeleton to open the channel's ion-conducting pore. If the force in the spring is F and the spring changes length Δx when the channel opens, then the energy difference between open and closed states is

$$\Delta G = \Delta G_0 - F \cdot \Delta x \quad \text{Eq. 1}$$

where ΔG_0 is the difference in the absence of force [9]. The larger the force, the lower the energy of the open state and the higher the channel's open probability. The ratio of open- to closed-state probabilities will increase e-fold per force $kT/\Delta x$, where kT is the Boltzmann constant times the absolute temperature. If $\Delta x = 4$ nm, then there will be an e-fold increase

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in gating ratio per 1 pN of force. Such a mechanism is also thought to operate in hair cells in the vertebrate ear [9], although the molecular identity of the channel is still not resolved [10]. A related mechanism operates for membrane-tension-sensitive ion channels, which respond to changes in cell pressure. In this case,

$$\Delta G = \Delta G_0 - \sigma \cdot \Delta a \quad \text{Eq. 2}$$

where σ is the membrane surface tension and Δa is the change in area of the channel [9]. For the bacterial MscL channels, which function as safety valves that protect the bacteria from osmotic pressure shocks, the pore is very large and, when it opens, the area increases ~10 nm^2. This accounts for the sensitivity of the channel, e-fold per surface tension change of 0.4 pN/nm [4].

The Piezo channels play roles in various mechanotransduction processes in both sensory cells (e.g. touch receptors [11] and nociceptors [12]) and non-sensory cells (e.g. red blood cells [13] and vascular endothelial cells [14]). In contrast to MscL channels, physiological studies show that the pore has a lower conductance and a higher selectivity to ions [4,8], indicating a smaller pore and therefore a potentially smaller Δa. If these channels were gated by the same mechanism as MscL, the sensitivity to membrane tension would be lower (e.g. a 10-fold smaller area change would require a 10 times higher tension change). However, the membrane surface tension in eukaryotic cells is thought to be much smaller than in osmotically shocked bacteria, with values ranging from 0.001 to 0.1 pN/nm in normal and highly swollen red blood cells, respectively [15], and 0.04 pN/nm in suspended fibroblasts [16]. So, how do the Piezo channels have high sensitivity to pressure and tension [17] despite their small pore size? The recent structures of mPiezo1 give hints about how this might be achieved.

In three recent studies, the structure of mPiezo1 was resolved at sub-4 Å resolution, which is sufficient to identify individual amino acid side chains (Figure 1A,B). The structures confirm an earlier lower-resolution cryoEM study [18] showing a propeller-like triskelion with three ‘blades’ surrounding a central module that includes a carboxy-terminal extracellular domain (CED), a pair of helical transmembrane domains and a triangular carboxy-terminal domain (CTD) (Figure 1B). One of the central transmembrane domains from each subunit forms the pore, which is closed in all of the cryoEM structures.

The new structures reveal a wealth of additional features [5–7]. Each propeller blade contains at least six helical units, each formed from four transmembrane helices (Figure 1A,B), and likely three more in the unresolved structure of the Piezo1 amino terminus, giving a total of 36 transmembrane helices per blade. Adding the two in the center gives a whopping 38 transmembrane helices for each of the three subunits! Remarkably, the propeller blades are not planar: instead, they lie on a spherically curved surface with the membrane bulging into the cytoplasm. Since the structure was determined in detergent in the absence of the bilayer, this may correspond to a ‘relaxed’ structure with high curvature. Importantly, though, when reconstituted in lipid vesicles, Piezo1 still forms a spherically

curved surface, a dimple, showing that the protein is sufficiently rigid to bend the lipid bilayer [5].

The protein contains two additional, remarkable structures. First are the 'parallel' amphipathic helices that are perpendicular to the transmembrane helices and likely insert part way into the membrane. They may play analogous roles to the amino-terminal helices of some BAR proteins (N-BARs) that contribute to membrane bending [19] and may maintain the static curvature of the channel in the lipid bilayer. Second, each domain contains a 10-nm long α-helix (the beam domain) that projects from the central domain and appears to buttress the first three transmembrane bundles.

How could such a structure sense changes in membrane tension? An ingenious hypothesis raised by Guo and MacKinnon [5] is that channel opening flattens the Piezo1 dimple, thereby increasing its projected area (Figure 1C). Because the structure is large (~20 nm in diameter) and the curvature is high (radius of curvature ~15 nm in the bilayer), the projected area change could be substantial (Figure 1C). For example, if the beam rotation is associated with pore opening, the area subtended by the first three transmembrane helical units could change by as much as 100 nm^2 (Δa). An even larger change is possible if the outer transmembrane helical units contribute to the area change. Thus, if the gating-associated area change is larger than it is for MscL, then Piezo1 can respond to smaller changes in the membrane tension despite a smaller pore size. In this way, by coupling gating to curvature change, the Piezo1 channel provides a new, highly sensitive mechanism to detect change in membrane tension.

The three-bladed propeller architecture is also mechanically interesting. Why three? A channel with only one or two symmetrical blades is expected to respond to tension changes primarily along one axis, while three blades is the minimum for omnidirectional sensitivity. The three blades suggest rotation: does rotation of the blades produce a counter-rotation of the center that opens the pore, as suggested in Zhao *et al.* [7]? The long blades hint at a large mechanical amplification so that a small change in membrane tension might be felt over a large membrane area.

The new structures of mPiezo1 raise many more interesting questions. How are conformational changes in the blades conveyed to the central domain and eventually to the channel pore? An open channel structure is needed. What is the curvature of the channel in cells? Electron cryotomography will be crucial. Is the gating of Piezo1 regulated by the intracellular cytoskeleton, such as the actin–spectrin network? Cell biological and *in situ* recording experiments on Piezo1 in cells are required. And can large changes in curvature and projected area be measured using biophysical techniques? Finally, do the new structures provide insight into the cellular physiology, for example shape homeostasis in red blood cells [13]? We are looking forward to the next installments.

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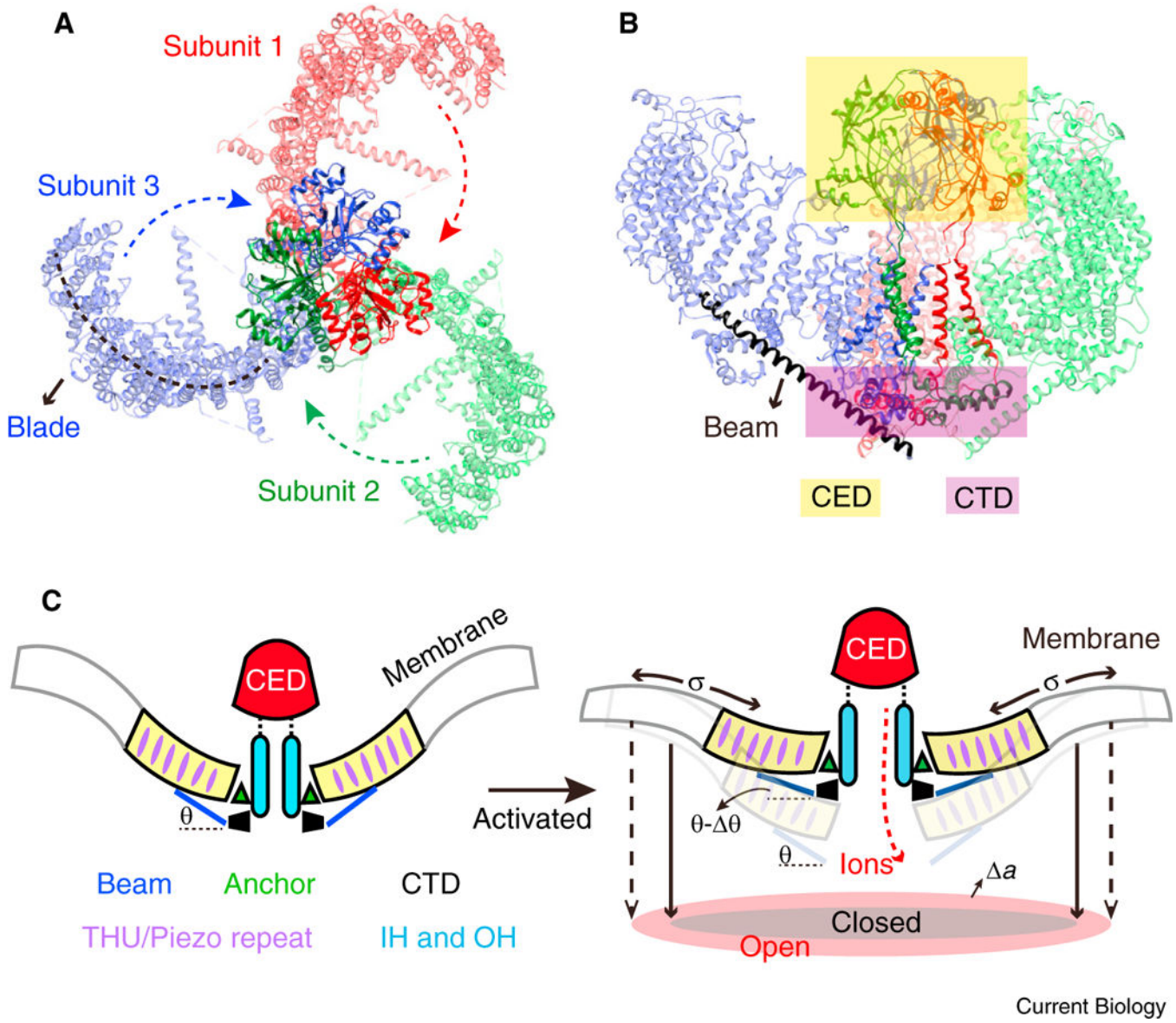

Figure 1. Structure and possible gating mechanism of the Piezo1 channel.

(A) Top view of the cryoEM-derived structure of the homotrimeric Piezo1: the three colors denote the three subunits; the dashed arrows indicate the interlocking of the three polypeptide chains such that the outer domain is connected to the opposite inner domain; and the dashed black line and the black arrow indicate one of three 'blades'. (B) Side view of Piezo1. CED in yellow denotes the carboxy-terminal extracellular domain, and CTD in purple denotes the carboxy-terminal domain. One of the three beam domains is labeled in black and indicated with an arrow. (A,B from PDB 6B3R.) (C) The curved blades of Piezo dimple the membrane into the cell (left panel). An increase in the membrane tension (σ) tends to flatten the dimple (right panel). As the dimple flattens, the angle (θ) between the beam and the flat membrane plane (beyond the channel) decreases ($\Delta\theta$), and the projected area of the channel increases (Δa) when the channel shifts from a closed (solid arrow) to an

open structure (dashed arrow). THU, transmembrane helical unit; IH, inner helix; OH, outer helix.