ETH zürich

Paper 4

Touch, tension, and Transduction: The Function and Regulation of Piezo Ion Channels

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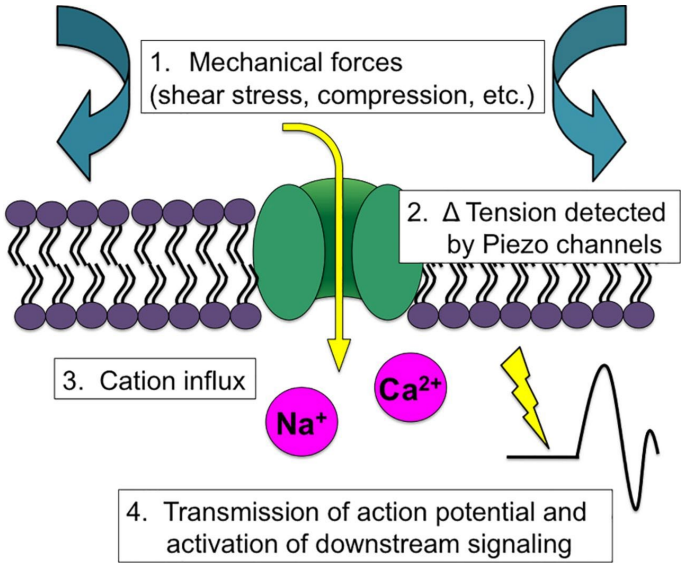
19.11.2019

What is a Piezo Protein?

- Pore-forming subunits of ion channels
- Open in response to *mechanical* stimuli
- Allowing positively charged ions to flow into the cell when open
- Two channel isoforms
  - Piezo1 and Piezo2
- No homologs identified in bacteria or yeast

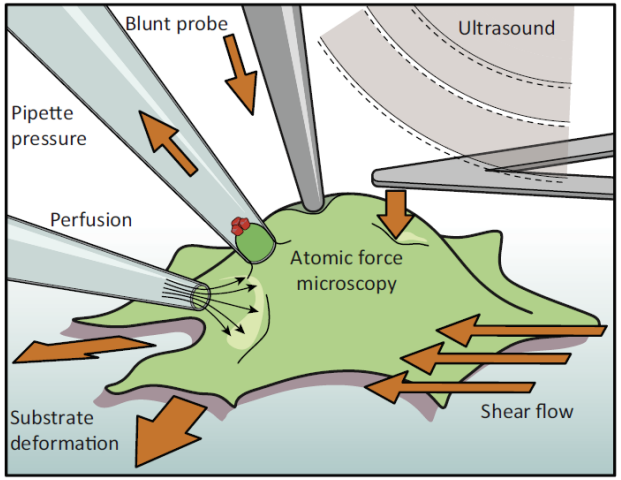


Mechanically Activated Ion Channel

- Form a channel
- Confer mechanically activated currents
- Expressed in mechanosensory cells (*in vivo*)
- Necessary and sufficient for mechanically activated currents in those cells (*in vivo*)

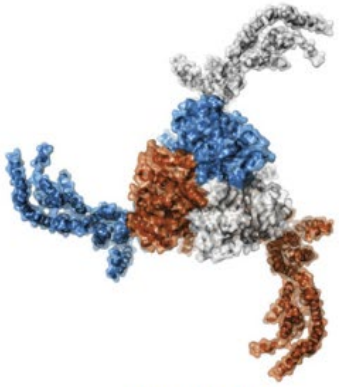
Activating Stimuli

- ‘Stretch’
  - Induces global membrane curvature
  - Reproducible pressure-response relationship
- ‘Poke’
  - Recruits varying number of channels
  - Inconsistent stimulus-response relationship
- Shear Stress
  - Superfusion pipette, microfluidic chamber
  - Activates Piezo 1
- Magnetic nanoparticles
  - Piezo 1

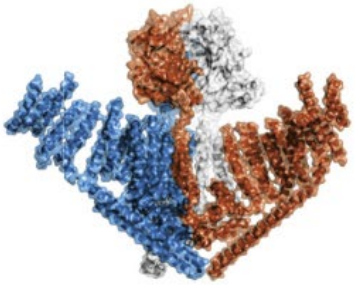


Channel Structure

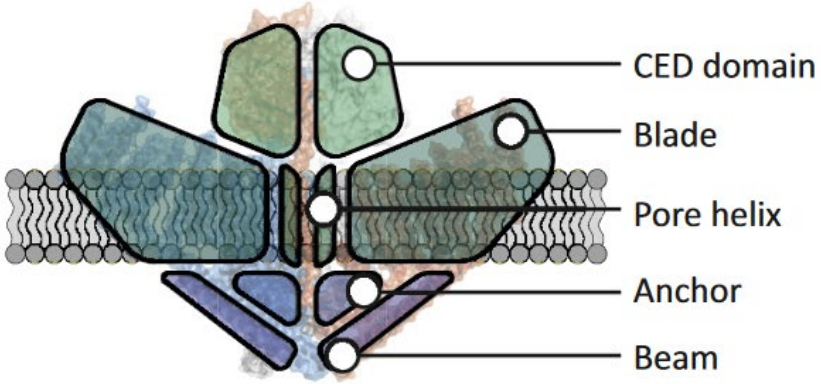
- Only available for Piezo1
- Propeller with three curved ‘blades’
- Central pore
- C-terminal extracellular domain (CED)



Top view



Side view



Activation Mechanism

- Different speculations
- Tethering channel to ECM or cytoskeleton
- Shear flow sensing
- Hydrophobic mismatch
  - Membrane curvature
  - Membrane thinning
- Interactions of membrane lipids

Mediation of Piezo Function

- Passive Modulation
  - Cytoskeletal Network
  - Lipid composition → Stiffness
  - Resting membrane tension
- Active Modulation
  - Mutations
  - Localized force application
  - Repeated applications of tension
  - Electrostatic interactions
- Passive or active
  - Yoda1, PIP2
  - G Protein-coupled pathways

Conclusion

- Little known about precise mechanisms for channel sensation
- Many mechanotransduction processes have not yet been explicitly tested
- Need development of new technologies