UC DAVIS HEALTH | SCHOOL OF MEDICINE

Department of
Physiology and Membrane Biology

Distinguished Lecture Series in Physiology

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"Multiscale molecular dynamics simulation studies of mechanosensitive Piezo1 channel"

Pacemaker The rapid conversion of mechanical forces into biological signals in vertebrates is commonly achieved by two mechanosensitive ion channels, Piezo1 and Piezo2. In the resting state, Piezos curve the surrounding membrane into an inverted dome shape. This unique dome shape has inspired biophysical studies on 1) how Piezo channels sense the force to open the pore; 2) whether and how Piezos cluster; 3) how to modulate Piezo functions using small molecules. Using all-atom molecular dynamics (MD) simulation of a single channel, we first show that Piezo1 dome flattening is correlated with the extracellular cap domain rotation and central pore dilation. The simulated gating motions, ionic conductance and selectivity consolidate many wild-type and mutant experimental data. To simulate multiple Piezo channels, we developed a minimal coarse-grained model to sample the spontaneous interactions between Piezo channels in the submicron scale membranes. Using this model, we investigated the propensity and topology of Piezo clustering under different channel densities, protein conformations, membrane bending rigidity, and membrane curvature. Finally, using MD simulations and electrophysiology, we identified a potential binding site of a small molecule Piezo1 agonist, Yoda1, at the transmembrane domain. We validated this binding site using state-dependent binding free energy calculations and identified two novel Piezo1 agonists with new scaffolds. In conclusion, our multiscale MD simulations provided valuable biophysical insights into the mechanical and chemical modulation of Piezo channels, hence paving the way toward using Piezo channels as promising therapeutic targets.

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GBSF and Zoom
12 p.m.

April
27

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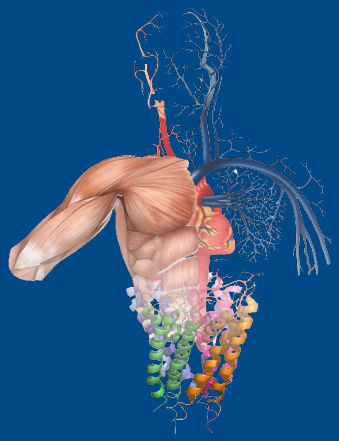

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