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Keynote 9, Prof Nieng Yan: How is electrical signal generated? Structural and mechanistic investigations of Nav channels

Friday 11 October 2019 09:00 (40 minutes)

The voltage-gated sodium (Nav) channels are responsible for the initiation and propagation of action potentials. Being associated with a variety of channelopathies, they are targeted by multiple pharmaceutical drugs and natural toxins. We determined the crystal structure of a bacterial Nav channel NavRh in a potentially inactivated state a few years ago, which is a homotetramer in primary sequence but exhibits structural asymmetry. Employing the modern methods of cryo-EM, we determined the near atomic resolution structures of a Nav channel from American cockroach (designated NavPaS) and from electric eel (designated EeNav1.4). Most recently, we have determined the cryo-EM structures of the human Nav channels, Nav1.2, Nav1.4, and Nav1.7 in complex with distinct auxiliary subunits and toxins.These structures reveal the folding principle and structural details of the single-chain eukaryotic Nav channels that are distinct from homotetrameric voltage-gated ion channels. Unexpectedly, the two structures were captured in drastically different states. Whereas the structure of NavPaS has a closed pore and the four VSDs in distinct conformations, that of EeNav1.4 and the human channels is open at the intracelluar gate with VSDs exhibiting similar "up"states. The most striking conformational differenc occurs to the III-IV linker, which is essential for fast inactivation. Based on the structural features, we suggest an allosteric blocking mechanism for fast inactivation of Nav channels by the IFM motif. Structural comparison of the conformationally distinct Nav channels provides important insights into the electromechanical coupling mechanism of Nav channels and offers the 3D template to map hundredes of disease mutations.

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