Research Highlight

Uncover the myths of voltage-gated sodium channels: cryo-EM structure of the EeNa$_v$1.4-β1 complex

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Uncover the myths of voltage-gated sodium channels: cryo-EM structure of the EeNa$_v$1.4-β1 complex

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Ion channels are membrane-embedded macromolecular pores, which allow charged ions flow through the insulating lipid bilayer when channel pores are opened. The opening and closing (termed gating) of ion channels are modulated by various stimuli, such as changes of membrane potential and binding of ligands (neurotransmitters, toxins, etc.). Some ion channels are classified as "voltage-gated ion channels", as they can be gated by altering the voltage difference across cell membrane. Various voltage-gated ion channels (specific to sodium ions, potassium ions, calcium ions, etc.) function collectively to amplify, transmit and generate electric signals in excitable cells (e.g., nerve and muscle cells), and therefore play a central role in neural signal tranduction, muscle contraction and other fundamental physiological processes [1].

Voltage-gated sodium (Na$_v$) channels are critical for generating action potentials. When stimulated by fluctuation of membrane potentials, they undergo three main conformation states (closed, open, and inactivated) to regulate the influx of sodium ions [1, 2]. Dysfunctional Na$_v$ channels have been implicated in a series of neurological and cardiovascular disorders. Notably, over 1,000 disease-related mutations have been identified in human Na$_v$ channels [3, 4]. Moreover, Na$_v$ channels are also major targets for drug development as natural toxins (scorpion venom, snake venom, tetrodotoxin, etc.) and clinical drugs (local anesthetics) act on them directly. However, despite their physiological importance and relevance to numerious diseases, structural elucidation of eukaryotic Na$_v$ channels at atomic or near-atomic level remains a highly challenging task, particularly due to the difficulty to obtain protein samples in sufficient quantity and purity. Recently, an exciting breakthrough has been reported in a study entitled "structure of the Nav1.4-β1 complex from electric eel", presenting a 4.0 Å cryo-EM structure of an eukaryotic Na$_v$ channel complex in an open state and revealing a potential allosteric blocking mechanism of fast inactivation [3].