第23回 細胞生理学セミナー/GTRセミナー

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“Structure of human GJC3 gap junction hamichannel at 2.3 angstrom resolution”

大学院創薬科学研究科 先端薬科学特論：単位認定講義

Connexin family proteins assemble into hexameric channels called hemichannels/connexons in the cell membrane, and two hemichannels from adjacent cells dock together to form a gap junction intercellular channel (GJICh). Although ions and small metabolites can freely diffuse through these channels in the open state, their permeability is finely regulated by various factors such as transjunctional/transmembrane voltage, divalentions, and membrane lipids. While previous studies suggested that the channel gating might involve dramatic conformational changes of N-terminal helices (NTHs) in connexin subunits, no clear evidence has been reported so far. Here we solve the cryo-EM structure of human Cx31.3/GJC3 hemichannel at 2.3 angstrom resolution. The structure reveals the entrance-lining conformation of NTH which is different from the pore-lining conformation shown in Cx26 and Cx46/50 GJIC structures. The conformational difference results in a smaller pore diameter (~8 angstrom) compared with those of GJIChs. The entrance-lining NTH conformation is mainly stabilized by the hydrophobic interaction of NTH with the second transmembrane helix. The residues involved in the interaction are highly conserved in half of connexin family proteins including Cx43 and Cx46, suggesting that these connexins may change the conformation of NTH from pore to entrance-lining for the channel permeability control.

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