Poster Presentation

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X-ray crystal structure of voltage-gated proton channel

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The voltage-gated proton channel, Hv1 (VSOP) has a voltage-sensor domain (VSD) but lacks an authentic pore domain, and the VSD of Hv1 plays dual roles of voltage sensing and proton permeation. Hv1 is required for high-level superoxide production by phagocytes through its tight functional coupling with NADPH oxidase to eliminate pathogens. Hv1 is also expressed in human sperm and has been suggested to regulate motility through activating pH-sensitive calcium channels. The activities of Hv1 also have pathological implications, such as exacerbation of ischemic brain damage and progression of cancer. In this study, our crystal structure of mouse Hv1 (mHv1) showed a “closed umbrella” shape with a long helix consisting of the cytoplasmic coiled-coil and the voltage-sensing helix, S4, and featured a wide inner-accessible vestibule. We also found a Zn^{2+} ion at the extracellular region of mHv1 protomer. The binding of Zn^{2+} strongly suggested that the crystal structure of mHv1 represents the resting state, since Zn^{2+} specifically inhibits activities of voltage-gated proton channels. Actually, two out of three arginines as sensor residues (R204 and R207) were located lower than the conserved phenylalanine, F146, on the S2 in a charge transfer center. This makes contrast with previous structures of other VSDs in the activated state where many positive residues of S4 were located upper than the conserved phenylalanine. Additionally, the crystal structure of mHv1 highlighted two hydrophobic barriers. Aspartic acid (D108), which is critical for proton selective permeation, was located facing intracellular vestibule below the inner hydrophobic barrier, thereby being accessible to water from the cytoplasm. Another hydrophobic layer of extracellular side probably ensures interruption of the proton pathway of mHv1 in resting state. These findings provide a novel platform for understanding the general principles of voltage sensing and proton permeation.

[1] *K. Takeshita, S. Sakata et al. Nat. Struct. Mol. Biol., 2014, in press,* ***[2]*** *Y. Fujiwara, T. Kurokawa et al. Nat. Commun., 2012, 3, 816 doi:10.1038/ncomms1823,* ***[3]*** *M. Sasaki, M. Takagi et al. Science, 2006, 312, 589-592*

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