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Structural insight of zink binding of Hv1/ VSOP in resting state

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The voltage-gated proton channel, Hv1 (VSOP)[1] has a voltage-sensor domain (VSD) but lacks an authentic pore domain. 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.

We succeeded to solve a crystal structure of chimeric construct of mouse Hv1 (mHv1) in the resting-state at 3.45 Å resolution[2]. Bijvoet anomalous Fourier map showed that a Zn2+ ion was bound at the extracellular region of Hv1 protomer. The binding of Zn2+ strongly suggested that the crystal structure of mHv1 represents the resting state, since Zn2+ specifically inhibits activities of voltage-gated proton channels. However, because of low resolution and high mobility of the crystal structure, binding mode of Zn2+ ions was not clear. FT-IR measurements of Zn2+ bound and unbound form and computational analysis revealed binding mode of Zn2+ in resting state.

[1] Sasaki, M. et al. (2006). Science, 312, 589-592.

[2] Takeshita, K. et al. (2014). Nature Struct. Mol. Biol., 21, 352-357.

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