Elucidating Zinc Binding to the Voltage-Gated Proton Channel hHv1 Using Computer Simulations

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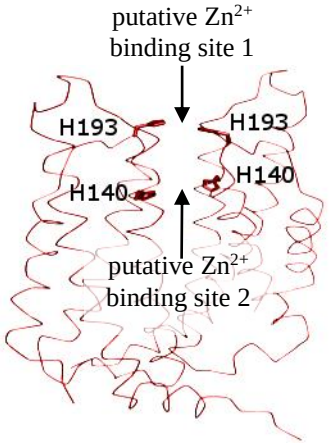

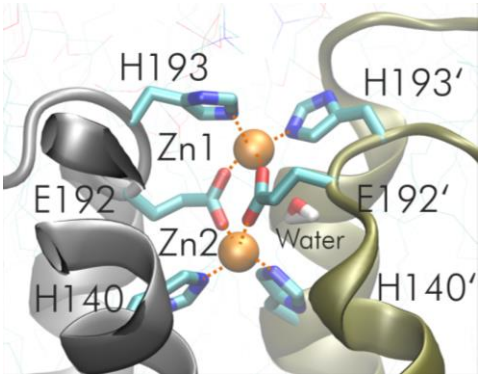

H_V1 voltage-gated proton channels are proton-specific ion channels with unique properties. For example, they are massively expressed in human sperm where they are necessary for maturation and motility, hence essential for conception.

Voltage-gated proton channels are strongly inhibited by Zn^{2+} and two histidine residues were found experimentally to be essential for Zn^{2+} binding. However, the two accessible histidine residues H140 and H193 are too far apart to coordinate simultaneously one Zn^{2+} in a structural model of the monomeric channel. It was thus hypothesized that two Zn^{2+} binding sites can be formed between pairs of equivalent histidine residues (H140–Zn–H140 and H193–Zn–H193) at the interface of a H_V1 homodimer. The consecutive experimental measurements were also in agreement with this hypothesis.

We tested this hypothesis and investigated the determinants of Zn^{2+} binding at the molecular level using computational approaches: molecular modeling, molecular docking, and molecular dynamics simulations.

Our results support the hypothesis enunciated above: The modeling and docking simulations show that the hH_V1 channels can form dimers that present an appropriate interface for two Zn^{2+} binding sites, each involving a pair of equivalent histidine residues from each monomer. The molecular dynamics simulations reveal that two Zn^{2+} can stably be accommodated in the proposed binding sites. The zinc ions are coordinated by the histidine and acidic residues. Essentially, the glutamate residues E192 play an essential role in Zn^{2+} binding. Comparison with another possible dimer conformation and with the monomeric form of the channel also reveals why the dimer conformation hypothesized above is more able to coordinate zinc ions.