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XFEL structures of the M2 proton channel of influenza A reveal pH-dependent water networks under room temperature conditions

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The M2 proton channel of influenza A is a drug target that is essential for replication of the flu virus. It is also a model system for the study of selective, unidirectional proton transport across a membrane. Ordered water molecules arranged in wires inside the channel pore have been proposed to play a role in the conduction of protons to the four gating His37 residues and the stabilization of multiple positive charges within the channel. Previous crystallographic structures determined using a synchrotron radiation source were biased by cryogenic data collection conditions, and room-temperature data collection was limited by radiation damage. These problems have been avoided through room temperature diffraction at an X-ray free electron laser. Data were collected at an XFEL source to a resolution of 1.4 Å at three different pH conditions: pH 5.5, pH 6.5, and pH 8.0. Here, we examine the ordering of water in the M2 pore within crystals containing only the C_{open} conformation, which is an intermediate that accumulates at high protonation of the His37 tetrad. This allows us to access multiple protonation states of His37 in the C_{open} conformation and probe changes in solvent ordering prior to and following the release of a proton into the viral interior. At pH 5.5, a continuous hydrogen bonded network of water molecules spans the vertical length of the channel, consistent with a Grotthuss mechanism model for proton transport to the His37 tetrad. This ordered solvent at pH 5.5 could act to stabilize the positive charges that build up on the gating His37 tetrad during the proton conduction cycle. The number of ordered pore waters decreases at higher pH, where the C_{open} state is less stable. These studies provide a graphical view of the response of water to a change in charge within a restricted channel environment.

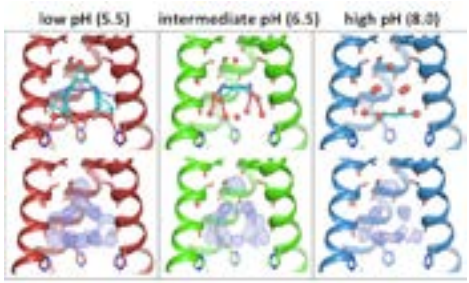

Figure1: *Room temperature XFEL structures of the M2 proton channel transmembrane domain at pH 5.5, 6.5, and 8.0. Solvent ordering is at a maximum at pH 5.5, with fewer ordered waters at pH 6.5 and pH 8.0. A continuous hydrogen bonding network is observed in the low pH condition and could be consistent with a Grotthuss transport mechanism for proton transport when the channel is at maximally conducting pH conditions.*

Biography

Jessica L Thomaston is a PhD candidate in the lab of Professor William DeGrado at the University of California, San Francisco. She studies the structure of the influenza M2 proton using lipidic cubic phase crystallization techniques and x-ray diffraction at synchrotron and XFEL sources. The M2 protein is among the smallest proton channels found in nature and is also a drug target against the flu. Her work focuses on the proton conduction mechanism of the M2 channel, particularly the involvement of water in proton transport and the structural characterization of how drugs and novel inhibitors bind to the channel and block proton conduction.

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