ATOMIC STRUCTURE AND GATING MECHANISM OF THE PATHOGENIC ENVELOPE PROTEIN FROM SARS-COV-2

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The Envelope (E) protein of SARS-CoV-2 is an ion channel essential for the assembly, maturation and egress of new virions. The E protein also disrupts the pH and calcium homeostasis in host cells leading to severe viral-induced inflammation. Studies in mice demonstrated that impairing the E function attenuates the pathogenic effects of SARS-CoV-2, highlighting the E channel as a promising antiviral target for treating COVID-19 symptoms. In this study, we employed advanced solid-state Nuclear Magnetic Resonance (ssNMR) methods to elucidate the structure and gating mechanism of the E protein ion channel domain (ETM) in lipid membranes.

Our ssNMR approach provided residue-specific configurations, contacts, hydration, and dynamics of ETM in lipids. We found that the ETM channels become dry at neutral pH (closed state) and hydrated at acidic pH with calcium (open state) (**Figure 1A**) [1]. The open state structure of ETM presents a pentameric α-helical barrel with a conical shape and a C-terminal 3_{10}-helix [2], whereas the closed state is shaped by a cylindrical barrel (**Figure 1B**) [3]. Notably, the open state presents a hydrophobic gate regulated by the sidechain of Arg38 that facilitates the passage of water at the C-terminal pore entrance (**Figure 1C**). We also identified extensive polar networks that regulate the opening and closing of the N-terminal pore. Our data indicates that channel hydration is tied to the conformational heterogeneity of the N-terminal polar network orchestrated by residues Glu8 and Thr9 [4].

These findings significantly advance our understanding of the pathogenic SARS-CoV-2 E ion channel, providing critical insights for the drug-design of E channel inhibitors. Moreover, our structural models shed light on the functional implications of the T9I mutation prevalent in Omicron variants, and offer generalised principles for modelling highly hydrophobic channels from other viruses.

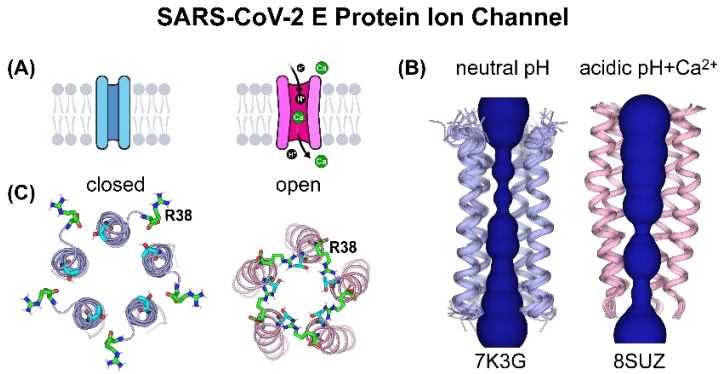

Figure 1: **(A)** ETM forms an ion channel that opens at acidic pH and presence of calcium ions. **(B)** ETM structures in the open (blue) and closed (pink) states. **(C)** In the closed state, the sidechain of Arg38 faces outwards of the channel, whereas in the open state it inserts into the pore.

References

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