UNIVERSITI TEKNOLOGI MARA

STRUCTURAL STUDIES OF TRANSIENT RECEPTOR POTENTIAL CHANNELS (TRPs) USING MOLECULAR MODELING AND DYNAMIC SIMULATION

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ABSTRACT

Transient Receptor Potential Canonical (TRPC) channel was the first group of TRP homologs that was cloned in mammals. The channel consists of seven subfamily members in this family. TRPC4 channels are nonselective cation channels permeable to Ca^{2+} that are expressed in various organs and cell types including numerous types of neurons, cardiovascular system, skeletal muscle cells, kidney, and immune cells. TRPC4 channels assemble into a tetrameric structure in the plasma membrane. The S4-S5 linker of TRPC4 has been shown to regulate the open-close of the channel by interacting with the S6 helix. Previous homology models that were built based on the potassium channel structure predicted inter-domain interactions were formed by G503 and the S623 between the linker with the S6 helix. Mutagenesis experiments of TRPC4 and TRPC5 supported that the mutation of the conserved glycine impaired the interaction, which resulted to the channel opening, and causing cell death due to the influx of Ca^{2+}. In this work, a tetrameric model of TRPC4 was built based on TRPV1 EM structure to study the role of S4-S5 linker in the channel gating. Molecular dynamics simulations were employed to describe the dynamics of the structure in a lipid bilayer environment. The simulations of both TRPC4 and TRPV1 native structures support the proposed interactions between the S4-S5 linker and the S6 helix. However, it was observed that D515 in the linker region formed hydrogen bonds with S623 during the simulation time. Similarly, in the TRPV1 simulations, D576 formed stable interactions with T685 in the S6 helix. Interestingly, simulations of $TRPC4_{G503S}$ mutant caused the selectivity filter region of the channel to open wider, while $TRPC4_{G503/S623A}$ mutant resulted to the channel conformation back as the native structure. Additionally, S508 and Y624 from S4-S5 linker and S6 helix formed hydrogen bonds during those mutant simulations. The thesis findings suggest the predicted residues in S4-S5 linker play a role in the channel conformation and function.

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