NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

SEMINAR

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Hosted by Prof J Sivaraman

Rotating and Gating: Molecular Mechanism of Human TRPM2 Opening



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Transient receptor potential (TRP) melastatin2 (TRPM2) is a cation channel associated with numerous diseases. It has a C-terminal NUDT9 homology (NUDT9H) domain responsible for binding ADP-ribose (ADPR), and both ADPR and Ca2+are required for TRPM2 activation. Here we report cryo-EM structures of human TRPM2, alone, with ADPR, and with ADPR and Ca2+. NUDT9H forms both intra- and inter-subunit interactions with the N-terminal TRPM homology region (MHR1/2/3) in the apo state, but undergoes conformational changes upon ADPR binding, resulting in rotation of MHR1/2 and disruption of the inter-subunit interaction. Ca2+binding further engages transmembrane helices and the conserved TRP helix to cause conformational changes at the MHR arm and the lower gating pore to potentiate channel opening. In my talk, I will talk about the molecular mechanism of concerted TRPM2 gating by ADPR and Ca2+.

Artwork by Ann Nee, DBS, NUS