

Modulation of human ORAI1 channels: modeling and simulations

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Orai1 is a calcium-selective channel located in the plasma membrane, and belongs to the family of calcium release activated channels (CRAC) [1]. Orai1, as component of store-operated calcium entry (SOCE), is activated by the second component of SOCE, STIM1, when intracellular calcium stores are depleted. STIM1, located at the endoplasmic reticulum (ER), senses levels of calcium in the ER and is activated by calcium store depletion. In turn, calcium influx via Orai1 channel refills calcium levels in the endoplasmic reticulum [2]. Based on the *Drosophila melanogaster* Orai crystal structure [3] a homology model of human Orai1 was prepared that includes extracellular and intracellular loops existing only in the human isoform [4]. The sequence and architecture of Orai channels is unique among other ion channels and suggests a novel gating mechanism. The selectivity filter is formed by a ring of six glutamate residues followed by a hydrophobic and consequent basic region further down the pore. The pore extends into cytosol by approximately 20 Å. Using combined experimental and theoretical approaches this study focuses on the central ion pore to investigate the gating mechanism of this unique channel including altered gating of Orai1 mutants occurring in tumor cells [6].

References

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