Closed and open structures of the eukaryotic magnesium channel Mrs2 reveal the auto-ligand-gating regulation mechanism

Ping Li[1#], Shiyan Liu[2], Johan Wallerstein[3], Rhiza Lyne E. Villones[4], Peng Huang[1], Karin Lindkvist-Petersson[1], Gabriele Meloni[4], Kefeng Lu[2], Kristine Steen Jensen[3], Sara I Liin[5] & Pontus Gourdon[1,6#]

[1] Department of Experimental Medical Science, Lund University, Sölvegatan 19, SE-221 84 Lund, Sweden

[2] Department of Neurosurgery, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, 610041, China

[3] Center for Molecular Protein Science, Department of Chemistry, Lund University, Naturvetarvägen 16, SE-223-62 Lund, Sweden.

[4] Department of Chemistry and Biochemistry, The University of Texas at Dallas, 800 W Campbell Rd., Richardson, TX 75080, USA

[5] Department of Biomedical and Clinical Sciences, Linköping University, SE-581 85 Linköping, Sweden

[6] Department of Biomedical Sciences, Copenhagen University, Maersk Tower 7-9, Nørre Allé 14, DK-2200 Copenhagen N, Denmark

[#] Corresponding authors: PL (ping.li@med.lu.se) or PG (pontus.gourdon@med.lu.se)

Magnesium (Mg^{2+}) is essential in physiology, and the most abundant cation in all organisms. The CorA/Mrs2 family of proteins are cardinal for influx of Mg^{2+} across cellular membranes. Mrs2 imports the cation to mitochondria in eukaryotes including humans. While it is established that CorA/Mrs2 members form symmetrical cone shaped homo-pentamers with a central pore in the closed state, the conducting and regulation mechanisms of permeation remain elusive, particularly for the eukaryotic Mrs2 members. Here, we report closed and open Mrs2 cryo-EM structures determined at overall resolutions of 2.6 and 3.2 Å, accompanied by functional characterization. In the open configuration, fully hydrated Mg^{2+} is likely concentrated at the pore entry, transferred partially hydrated to the GMN selectivity motif, and flux then permitted by a narrow hydrophilic pore, as driven by electrochemical gradients. Permeation is dictated by positively charged and hydrophobic residues that seal the end of the channel. The reversible transition between the closed and open conformations is orchestrated and regulated by two pairs of conserved sensor-serving Mg^{2+}-binding sites in the matrix lumen, located in-between monomers in the soluble domains, thereby stabilizing the closed conformation. At lower levels of Mg^{2+}, these ions are stripped permitting an alternative yet symmetrical shape, maintained by the RDLR-motif that replaces one of the sensor site pairs in the open state. Collectively, our findings thus establish the molecular basis for selective Mg^{2+} influx of the eukaryotic Mrs2 channel and an auto-ligand-gating regulation mechanism. Similarities and differences between CorA proteins present in prokaryotes and Mrs2 are also highlighted that may have bearing for drug-discovery efforts.