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Insights into the debated gating of mtCU using computational modelling

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The identification of the molecular components making up the mitochondrial Ca^{2+} uniporter complex (mtCU) began appearing in 2010. Nevertheless, there is currently a lack of understanding of the structural mechanisms underlying the mitochondrial Ca^{2+} uniporter dominant-negative beta (MCUb) inhibitory function despite high homology to the well-studied pore forming MCU subunit. Models of channel gating are highly debated based on cryoEM structures and electrophysiology data. Thus, we aimed to reveal the structural basis for the debated gating mechanism of the mtCU channel and how MCUb inhibits this gating through homology modeling. Instead of a direct occlusion model, we speculate increased open probability of the channel occurs in high Ca^{2+} due to Ca^{2+}-dependent structural changes in the mitochondrial Ca^{2+} uptake (MICU) gatekeeping subunits, which allosterically couple to the luminal gate of MCU via the essential MCU regulatory subunit (EMRE).