A dynamical perspective on SERCA inhibition by Phospholamban

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The P-type Sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) pumps calcium ions into the sarcoplasmic reticulum, initiating myocyte relaxation and refilling the reticulum in preparation for the next contraction cycle. In cardiac muscle, SERCA is controlled by a small transmembrane protein called Phospholamban (PLN). SERCA inhibition is released by cAMP-dependent phosphorylation of PLB at Serine 16 by Protein Kinase A.

Despite significant efforts, the mechanistic details of PLN inhibition have not been completely elucidated. Aimed to address this problem, we performed an exhaustive structural comparison among all the structures of the SERCA pump so far reported and conducted a series of coarse-grained molecular dynamics simulations on the SERCA-PLB complex. In the non-phosphorylated state, PLB increases significantly the mobility of the Nucleotide-binding Domain of SERCA, which samples conformations alike those typical for the E1 state and increasing the global tilt of the pump to the membrane normal. Upon Ser16 phosphorylation, differential interactions between the cytoplasmic Domain of PLN the membrane impair SERCA-PLB interactions, driving SERCA to sample conformations alike those of the isolated pump in E2 state. Worthy, protein-protein interactions at the rim of the membrane involve one of the Tryptophan residues that govern the tilt of SERCA, which is not present in homologous P-type ATPases. We conclude that instead of a key-lock mechanism, PLB reshapes the free energy landscape of SERCA modifying also the interplay with the phospholipid bilayer.