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Effects of Sarcolipin on Ca^{2+} pump SERCA1a enzymatic cycle studied by normal mode analysis

The Ca^{2+} pump SERCA1a is a P-type ATPase, localized in the sarcoplasmic reticulum membrane of striated muscle cells. SERCA1a is involved in the contraction/relaxation process by fast pumping the cytoplasmic Ca^{2+} into the reticulum. Throughout its catalytic cycle, SERCA1a presents two major conformations: the E1 conformation where its Ca^{2+} channel is open toward the cytoplasm and the E2 conformation where this channel is open toward the lumen. This conformational transition is enhanced by ATP phosphorylation which occurs after Ca^{2+} binding by SERCA1a. Sarcolipin (SLN), a transmembrane helix of 31 residues regulates SERCA1a by diminishing its affinity to Ca^{2+}. The mechanism of this regulation is not elucidated yet despite the knowledge of the crystal structure. To decipher this mechanism, we performed Normal Mode Analysis (NMA), in the all-atom model on two systems, in the presence and the absence of SLN, in a POPC membrane and one layer of water for the soluble parts of the protein. This analysis showed that both systems are prone to go toward the confirmation of $2Ca^{2+}$ E1 more easily than toward that of E2. However, both transitions seem more difficult in the presence of SLN, because of some specific interactions with SERCA1a that result in additional fluctuations of SERCA1a-SLN. A long-distance transmission of information (over 35 Å) within the protein was also observed, explaining the phosphorylation difficulty in the complex. These results provide new insights into the mechanism of the SERCA1a enzymatic cycle and its regulation by SLN.

Biography

Liliane Mouawad was always interested in understanding the mechanism of action of proteins or protein assemblies. This understanding may be based on either molecular simulations or on experiments like NMR. But her expertise is primarily in molecular dynamics simulations and more precisely in normal mode analysis (NMA). She has developed several methods going from the calculation of normal modes of very large systems or of images, to the calculation of the pathway between two protein conformations, or to the prediction of the compactness of a calcium-binding protein. Recently she was also involved in docking and virtual screening themes, where she has acquired enough expertise to develop a new consensus methodology to overcome some issues observed in these approaches.

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