Comparing the fluctuations of the intrinsically disordered C-terminal domain of human SELK free in water and in lipid membrane

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SELK is a single-pass trans-membrane protein that resides in the endoplasmic reticulum membrane (ER) with a C-terminal domain exposed to the cytoplasm that is known to interact with different components of the endoplasmic reticulum associated to the protein degradation (ERAD) pathway. This protein is resulted to be up-expressed in hepatocellular carcinoma and in other cancers, therefore there is a need to analyze its structure-function relationships. In this work we performed a detailed analysis of the C-terminal domain sequence of SELK, modeled its three-dimensional structure and analyzed its conformational changes by Molecular Dynamics simulations.

Our analysis showed that the C-terminal domain of SELK is a weak polyelectrolyte and specifically, a polycation, which has the characteristic molecular signature of natively disordered segments. Since the search by BLAST has not evidenced possible templates with an acceptable sequence identity percentage with the C-terminal sequence of SELK, its three-dimensional structure was modeled by *ab initio* modeling. The best model is characterized by one short helix and the most part of residues with no regular secondary structure elements. This model was subjected to MD simulation at neutral pH in water to assess the stability of the modelled structural organization free in solution. To deepen the structural analysis of the C terminal domain, we have also studied the organization of the whole protein inserted into the membrane by a procedure of comparative modeling between fold recognition and folding ab initio. Then, the complete structure of SELK was subjected to MD simulations in the lipid bilayer and a water box.

Analyzing the MD trajectories, we found that the C-terminal domain of SELK is still highly mobile during the simulation in water-lipid bilayer by showing a decrease of the structural compactness, a lesser number of H-bonds, as well as a higher value of the total void volume and of the total solvent accessible area compared to the simulation in only water system. However, in both the simulations this region is stabilized mainly by a marked number of H-bonds, and pi-cation and IAC interactions, which suggest a globule organization very different from the classic globular one. Furthermore, water-protein interaction data suggest, as for other IDPs, that the hydration water tends to cluster around the protein facilitating its organization to globule.