Dynamics of Translocator protein

Translocator protein (TSPO) is a transmembrane (TM) protein localized in outer mitochondrial membrane. It consists of five transmembrane helices connected by loops of various lengths. TSPO has been implicated in various pathological situations that include cancer, Alzheimer's and Parkinson's diseases, malaria, inflammation, etc. Initial studies indicated that TSPO would be involved in transport of cholesterol from cytoplasm into the inner membrane of mitochondria. Furthermore, a cholesterol-binding site, the so-called CRAC motif was identified. Yet, recent studies have brought contradictory results and led to revisit the actual role of TSPO. Hence, its physiological role remains still unclear.

Recent high-resolution structures of TSPO solved for different species in different conditions exhibit significant differences, which confirms that TSPO is a dynamical protein. In the present study, we examine the structural dynamics of the mouse TSPO (mTSPO) protein by means of coarse-grained and all-atom molecular dynamics simulations. As mTSPO 3D structure was only solved in the presence of the PK-11195 ligand, we address the following questions: i) what is the structure and the dynamics of the protein in the absence of the ligand ii) what is the impact of the ligand on the dynamics of the protein. Our results show that in absence of ligand TSPO is a highly dynamic protein, characterized by secondary structure deformations. These results are in very good agreement with solid-state NMR data obtained in the absence of the ligand. In the presence of the ligand, the secondary structures are more preserved, which confirms the stabilizing effect of the ligand. However, surprisingly, the protein exhibits larger fluctuations in the loop regions when the ligand is present. Importantly, we also identified correlated motions between TM helices that differ when TSPO is bound or not to PK-11195. Notably, this ultimately influences the dynamics of the cholesterol-binding CRAC motif. We further propose that these changes in dynamics would have impact on binding properties of TSPO, e.g. binding to cholesterol, or to other proteins that are believed to interact with TSPO as part of various physiological processes.