



Contribution ID: 66

Type: Poster

Effect of amphiphilic environment on the solution structure of mouse TSPO translocator protein

The translocator protein (TSPO) is a ubiquitous transmembrane protein of great pharmacological interest thanks to its high affinity to many drug ligands. The only high-resolution 3D-structure known for mammalian TSPO was obtained by NMR for the mouse mTSPO in DPC detergent only in presence of the high-affinity PK 11195 ligand. An atomic structure of free-ligand mTSPO is still missing to better understand the interaction of ligands with mTSPO and their effects on the protein conformation.

In the present study, we decipher the solution structures of the recombinant mTSPO without ligand both in (i) SDS, the detergent used to extract and purify the protein from *E. coli* inclusion bodies, and (ii) DPC, the detergent used to solve the PK 11195-binding mTSPO NMR structure.

We report partially refolded and less flexible mTSPO helices in DPC compared to SDS. Besides, DPC stabilizes the tertiary structure of mTSPO, as shown by a higher intrinsic Trp fluorescence and changes in indole environment.

We evaluate by SEC-MALLS that ~135 SDS and ~100 DPC molecules are bound to mTSPO. SEC-small-angle X-ray (SAXS) and neutron (SANS) scattering confirm a larger mTSPO-detergent complex in SDS than in DPC. Using the contrast-matching technique in SEC-SANS, we demonstrate that mTSPO conformation is more compact and less flexible in DPC than in SDS. Combining *ab initio* modeling with SANS, we confirm that mTSPO conformation is less elongated in DPC than in SDS. However, the free-ligand mTSPO envelope in DPC is not as compact as the PK 11195-binding protein NMR structure, the ligand stiffening the protein.

Preliminary results on reconstructed mTSPO in stealth POPC nanodics (i.e. contrasted in SANS), show protein dimerization, as already suggested in the literature under more native conditions.

Session

Structural biology

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Session Classification: Clip Session