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Deciphering membrane protein structures through scattering and modeling: insights into TSPO, a neuroimaging key marker

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Membrane proteins play essential roles in cellular function and are prime therapeutic targets, yet their structural characterization remains a major challenge. Despite advances in artificial intelligence, including AlphaFold, accurately predicting their structures is still difficult. These proteins make up 30% of the proteome and 60% of drug targets, yet they are vastly underrepresented in the PDB, with only 3% of resolved structures. This is largely due to the challenge of maintaining their native state in amphiphilic environments, limiting the applicability of classical structural techniques such as X-ray crystallography, NMR, and cryo-EM.
To overcome these limitations, we combine small-angle X-ray and neutron scattering (SAXS/SANS) with ab initio modeling, offering a powerful approach to study membrane proteins under near-physiological conditions. We apply this methodology to TSPO (Translocator Protein), a highly conserved transmembrane protein with strong pharmacological relevance, particularly in neuroimaging.
Our study explores the solution structures of mouse TSPO (mTSPO) in various amphiphilic environments to unravel its structure/function relationships: (i) SDS, the detergent used for its solubilization from E. coli inclusion bodies, where mTSPO is stable and monodisperse but nonfunctional ; (ii) DPC, the detergent used to determine its NMR structure, where a stabilizing ligand enhances rigidity and induces µM affinity ; (iii) membrane-mimetic environments (DPC/DMPC bicelles), where optimized refolding restores nM affinity, approaching its native functional state.
By deciphering the structural behavior of mTSPO across these conditions, our work provides valuable insights into its function, paving the way for the development of new pharmacological molecules for diagnostics and therapeutics.

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