Probing conformational differences between the structures of WT- and mutant ΔF508 Cystic Fibrosis Transmembrane Conductance Regulator

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The cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel is a membrane-integral protein that belongs to the ATP-binding cassette super-family. Mutations in the CFTR gene cause cystic fibrosis in which salt and water are defective in various tissues. To investigate the conformation of the CFTR, we applied the small-angle x-ray scattering (SAXS) technique on recombinant wild type (WT) CFTR and on CFTR carrying the ΔF508 mutation purified from yeast. Extrapolation of the SAXS spectra to the origin suggested that the WT-CFTR was monodisperse, with a molecular mass near that accounts for one CFTR molecules and 251 molecules of detergent. The pair distance distribution function, $P(r)$, is consistent with a globular scattering particle composed by multiple shells, that is compatible with a protein inside a detergent micelle. The CFTR mutant ΔF508 shows a significantly different spectrum, with a smaller gyration radius. $P(r)$ is also consistent with a multi-shell globular particle, but with a structure different from WT-CFTR. We present here the first direct evidence observations of the WT and mutant CFTR conformations, showing that the WT- and ΔF508-CFTR structural features appear to be significantly different, possibly indicating a different co-translational folding of these two isoforms.

The formulation of three-dimensional studies of the CFTR structure based on SAXS results is in progress.