MOLECULAR DYNAMICS OF CFTR: Structural stability and thermodynamics of the first nucleotide binding domain (NBD1)

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Motivation

The CFTR (Cystic Fibrosis transmembrane Conductance Regulator), a membrane protein expressed in the epithelium, is a chloride channel for. Mutations in the cftr gene cause a chronic, developmental and hereditary disease, known as Cystic Fibrosis. The most common mutation is the deletion of F508, the residue present in the first nucleotide binding domain (NBD1).

Methods

In our work we have study the thermodynamic properties of NBD1 normal (wt) and mutant (dF508), starting from the crystallographic structures from the Protein Data Bank using the techniques of Molecular Dynamics.

Results

The two structures were similarly stable at room temperature, showed no change enthalpy or entropy, maintaining the same dimantions and the same order of magnitude of atomic fluctuations; the only difference was the energy of interaction with the solvent, in which the mutant appears slightly disadvantaged. At microscopic level, the two models showed local variations (in residues at 8 Å from F508) of the surface exposed to the solvent and the loss of a contact (M469) and a hydrogen bond (T465) with ATP in the mutant compared to wt. We also found a decrease in the mutant of about 30 times of affinity for ATP compared to wt. The study of molecular models makes possible to investigate microscopic differences, provides a valuable aid for the formulation of hypotheses on the mechanisms of ligand-receptor interaction and provides the opportunity to explore strategies to correct defects, through the rational design of drugs.

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