Journal club

Restoration of function of the ΔF508 mutation in cystic fibrosis

The first nucleotide binding domain (NBD1) of the of ΔF508 cystic fibrosis transmembrane conductance regulator (CFTR), is considered a potential drug target in cystic fibrosis but the links between this and CFTR misfolding remain unclear. NBD1 is one of the cytosolic domains of CFTR and is found in at least one allele of 90% of cystic fibrosis patients, significantly diminishing the folding efficiency of CFTR. The aim of this study was to clarify the role of NBD1 and structural consequences of the ΔF508 mutation in CFTR assembly.

The isolated domains of thermodynamic and kinetic destabilisation from isolated NBD1 variants by the ΔF508 mutation were studied along with conformational stabilisation of ΔF508 NBD1. Thermodynamic and kinetic destabilisations in combination were shown to be responsible for the ΔF508 NBD1 misfolding. In full-length CFTR, the stability of NBD1 and NBD1-CL interface is needed for normal channel function. As ΔF508 causes impairment of both these domains, energetic and interface defects (NBD1-MSD2) need to be corrected simultaneously in ΔF508 CFTR for wild-type function.

This study explains the limitations of some corrector molecules when targeted against a particular structural abnormality in CFTR. The understanding of interface mutation in such complicated multi-domain membrane proteins may lead to structure based combination corrector therapies.

► **Rabeh WM,** Bossard F, Xu H, *et al*. Correction of both NBD1 energetics and domain interface is required to restore ΔF508 CFTR folding and function. *Cell* 2012;**148**:150–63.

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