Structures of CFTR NBD1 Suggest a Molecular Mechanism for Cystic Fibrosis

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Cystic fibrosis (CF) is caused by genetic defects in the cystic fibrosis transmembrane conductance regulator protein (CFTR), most commonly through omission of residue Phe-508 (ΔF508) in the first nucleotide-binding domain (NBD1), resulting in misfolded, non-functional CFTR chloride channel. The structure of NBD1 was solved in order to better understand the effect of this deletion.

Initially, the structure of wild-type (WT) mouse NBD1 was determined [1]. This revealed a largely conventional NBD fold, compared with those of similar bacterial proteins, with the exception of additions in the N- and C-terminal regions of the protein with phosphorylatable and potentially regulatory function. Residue Phe-508 was seen to be surface exposed in a loop region and not of obvious importance to the NBD1 fold.

Recently, the structure of human NBD1 with ΔF508 present was determined [2], which revealed that the deletion did not alter or disrupt the fold of this domain. This observation was supported by thermodynamic measurements on WT and ΔF508 protein that showed the stability of NBD1 is unaffected as well. The effect of the deletion then appears to be the disruption of interactions of NBD1 with other domains of CFTR, most likely with the first membrane spanning domain (MSD1). This new understanding of the molecular mechanism of dysfunctional ΔF508 CFTR will lead to improved drug discovery efforts for CF.

[1] Lewis H.A., Buchanan S.G., et al., *EMBO J.*, 2004, **23**, 282. [2] Lewis H.A., Zhao X., et al., *J. Biol. Chem.*, 2005, 1346.

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