

SFB 35 Colloquia in Membrane Transport

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"Correcting the Trafficking Defect of Mutant CFTR"

The main cause of Cystic Fibrosis (CF), one of the most common life-shortening recessive genetic diseases, is the F508del mutation, a deletion of 3 nucleotides in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. CFTR (also ABCC7) is a cAMP-activated chloride (Cl⁻) channel expressed at the apical membrane of most surface epithelial cells, like the airways, the gastrointestinal tract, and in cells lining the ducts of several glands, like the sweat gland, the pancreas and the submucosal glands. Due to the absence/impairment of functional CFTR in epithelia of CF patients very little or no CFTR-mediated Cl⁻ transport is generally observed. The molecular and cellular defects associated with the most prevalent mutation (F508del), is at the level of CFTR intracellular localization, since the mutant protein fails to traffic to the plasma membrane, being mostly retained and degraded at the level of the endoplasmic reticulum (ER) [1,2,3]. The focus of this talk will be on the mechanisms of the ER quality control which are responsible for the intracellular retention of F508del-CFTR as well as on the pharmacological strategies to rescue this mutant by promising therapeutic small molecules which have started to emerge from the research to the clinical setting [4].

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References:

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2. Roxo-Rosa M, Xu Z, Schmidt A, Neto M, Cai Z, Soares CM, Sheppard DN, Amaral MD (2006) Revertant mutants G550E and 4RK rescue cystic fibrosis mutants in the first nucleotide-binding domain of CFTR by different mechanisms. *Proc Natl Acad Sci USA* 103, 17891-17896.

3. Scott-Ward TS, Amaral MD (2009) Deletion of F508 in the first nucleotide binding domain of CFTR increases its affinity to bind the Hsc70 chaperone. *FEBS J* 276, 7097-7109.
4. Amaral MD, Kunzelmann K (2007) Molecular targeting of CFTR as a therapeutic approach to cystic fibrosis. *Trends Pharmacol Sci* 28: 334-341.