

A30

Regulation of CFTR expression and function by NOS isoforms

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Background

The cystic fibrosis transmembrane conductance regulator (CFTR) is the gene of interest in the eponymous disease, cystic fibrosis (CF). CFTR is expressed in epithelial cells and functions as a chloride channel. Several hundred mutations are known to occur in CF patients, but the most prevalent mutation is the deletion of phenylalanine at position 508 ($\Delta F508$). Although the mutated protein is retained in the endoplasmic reticulum, the channel has been shown to be at least in part functional. A possible strategy for the treatment of CF therefore aims at facilitating surface expression by e.g. increasing total protein expression or by chaperoning the protein on its route from the endoplasmic reticulum to the cell surface. Polymorphisms in nitric oxide synthase (NOS) have been shown to influence disease severity in CF patients. Insights into the molecular mechanisms underlying the disease modifying effect of NOS will not only help understanding variation in the clinical course of cystic fibrosis but it may also provide information that can be exploited to improve and individualize treatment strategies for CF patients.

Results and conclusions

Using cell culture systems, we have investigated the effect of NOS on CFTR expression levels. Preliminary results show an up-regulation of wild-type and mutant CFTR by two NOS isoforms. This CFTR up-regulation is independent of the enzymatic activity of NOS. Deletion of a C-terminal PDZ domain interaction motif (TRL) does not block NOS-mediated increase in CFTR expression. In future experiments we will investigate if the observed up-regulation of CFTR is mediated via a direct or indirect interaction and if this enhanced expression translates into a higher level of functional chloride channels formed by CFTR $\Delta F508$ at the cell surface.