Proposal for MSc Thesis

Regulation of CFTR membrane stability – cross-talk between signalling pathways and the cytoskeleton

Supervision: **Carlos M Farinha** (cmfarinha@fc.ul.pt)

Host unit: Functional Genomics and Proteostasis (FunGP) lab, BioISI - Biosystems & Integrative Sciences Institute, FCUL (C8 Bldg)

Background

CF, the most frequent fatal recessive disease among Caucasians, is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, encoding a cAMP-stimulated Cl- channel at the apical plasma membrane (PM) of epithelial cells. The most common mutation (occurring in ~ 90% of CF patients) F508del, leads to F508del-CFTR protein retention in the ER and premature degradation, due to inefficient folding which is recognized by the ER quality control (ERQC)[1].

Although some drugs are available that target the misfolding of the protein – promoting its relocation to the PM – or its gating defect – promoting its opening, PM-rescued CFTR still exhibits an accelerated turnover due to either increased endocytosis or decreased recycling. This stability defect is still not totally understood and exploited in terms of therapeutic potential[1,2].

CFTR regulation at the PM depends on multiple components, being cAMP one of the most relevant. CFTR regulation at the plasma membrane is facilitated by tethering of PKA in the vicinity of CFTR through the scaffolding proteins ezrin and NHERF1. Correct compartmentalization of PKA and cyclic AMP has been shown to be necessary for proper regulation of CFTR function.

Our work has shown that the cyclic AMP sensor Epac (exchange protein directly activated by cyclic AMP) interacts, directly or indirectly, with CFTR, and that activation of Epac with a specific agonist causes an increase in CFTR levels in human respiratory cells thorugh a decrease of its endocytosis[3].

Recent unpublished work has shown that the regulation of CFTR by Epac relies on the formation of macromolecular complexes that involve several actin cytoskeleton regulators that contribute to the fine tuning of CFTR PM levels.

Objective: The aim of this MSc thesis plan is to characterize the role of the actin cytoskeleton in the regulation of CFTR at the PM by cAMP.

Specific questions to be addressed include…

- Dissecting the mechanism through which actin cytoskeleton regulators impact PM CFTR
- Assessing the impact of modulation of cytoskeleton regulators upon CFTR function and its relationship with cAMP signalling/Epac activation
- Assessing the impact of modulation of cytoskeleton regulators upon rescue of mutant CFTR

References

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