A unifying network regulating CFTR trafficking and function

Place of work/: RNA Systems Biology Lab & Cystic Fibrosis Research Lab, BioISI, FCUL

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Background and objective

Most Cystic Fibrosis is caused by the deletion of F508, that results in retention of the mutant protein within the ER. This is due to the interaction of immature forms of CFTR with ERQC proteins, which target misfolded conformations for proteasomal degradation. Although many (large scale) studies have addressed CFTR protein-protein interactions, a unifying approach to reconcile such information is lacking. Here, we propose to use network analysis combining the available omics studies in the field to determine the most relevant pathways in the regulation of CFTR trafficking and function. This work will explore the strong expertise of the supervising team and host labs in network biology and CFTR trafficking (as shown in previous publications – see below).

Workplan

To fulfil this objective, the work proposed involves:

1. Data collection – Identification of the relevant studies to be included and collect the data previously published that is relevant to the identification of the proteins expressed, interacting or regulating CFTR trafficking.
2. Network construction - An integrated network will be assembled including: CFTR; CFTR interactors (retrieved from the studies described above); Proteins associated with other rare conformational diseases (retrieved from DisGeNet and Open Targets); Proteins involved in protein trafficking pathways; Minimum number of proteins needed to link all the previous proteins in a connected network, using protein interactions retrieved from public databases (APID, HuRI, StringDB).
3. Network mining – Development of protein metrics that integrate 1) gene or protein expression measurements, 2) type of experiment or cellular model where interactions were detected, 3) connectivity to other conformational disease associated proteins, 4) network centralities and 5) functional annotation. These metrics will be used to prioritize the most relevant network nodes which may have a higher impact in the regulation of CFTR trafficking.
4. Validation of the network and protein candidates obtained – If time allows, and to validate the obtained network, we will select the most relevant nodes and pathways identified and pick 10-20 proteins whose down-regulation will then be assessed in terms of F508del-CFTR exit from the ER (assessed by Western blot, fluorescence microscopy and iodide efflux assay).