Protein Folding and Misfolding in Cystic Fibrosis

Douglas M. Cyr, Diane Grove, and Meredith F.N. Rosser

Department of Cell and Developmental Biology; University of North Carolina; School of Medicine; Chapel Hill, NC 27599

CFTR is a polytopic membrane protein that functions as a Cl- channel and consists of 2 membrane spanning domains (MSD), 2 cytosolic nucleotide binding domains (NBD) and a cytosolic regulatory domain. The mechanism for CFTR folding is complex and the mode by which disease related CFTR mutants are selected for premature degradation is not clear. To gain insight into these issues and develop drug to treat Cystic Fibrosis we are identifying the steps in CFTR folding that are facilitated by cytosolic and ER localized chaperones. In addition, we identified the Hsc70/CHIP complex and the Rma1/Derlin complex as cytosolic and ER membrane associated E3 ubiquitin ligases that cooperate to select misfolded CFTR for degradation. Recently, we investigated the role which ER lumenal calnexin plays in CFTR folding. In parallel, we probed the mechanism by which deletion of F508 arrests CFTR folding. Calnexin was found to be required for proper assembly of CFTR's membrane spanning domains (MSDs), which is also required for completion of down stream folding events that involve NBDII. Interestingly, CFTR?F508 exhibited biogenic defects that occurred both before and after the calnexin dependent step in CFTR folding. The RMA1 E3 ubiquitin ligase appeared to detect defects in MSD assembly, where as recognition of misfolded NBDII is mediated by the Hsc70/CHIP E3. Chemical correctors were observed to alter the conformation of specific sub-domains of CFTR and enable it to selectively pass through either the CHIP or Rma1 quality control checkpoints. Models that describe the mechanism by which chemical correctors enable CFTR?F508 to escape ER quality control will be discussed.
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