Profiling the Effects of Molecular Chaperones on the Pharmacological Properties of Pathogenic CFTR Variants

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Cystic Fibrosis (CF) is a genetic disease caused by mutations that impair the folding and/ or function of the Cystic Fibrosis Transmembrane Conductance Regulator chloride channel (CFTR). The most prevalent mutations compromise CFTR folding and enhance its quality control (QC)-mediated degradation in the endoplasmic reticulum. These conformational defects alter the interaction of the CFTR protein with various molecular chaperones in a manner that tips the balance between its synthesis and degradation. Recent interactome profiling experiments have identified several molecular chaperones that shape both the expression of CF variants and their response to small molecule pharmacological chaperones that are currently approved to treat CF. However, the specific chaperones that modulate expression and therapeutic rescue differ among CF variants. To identify variants that share common QC mechanisms, we first used deep mutational scanning to compare the plasma membrane expression and pharmacological response of a near-complete catalog of 237 known CF variants in HEK293T cells. To determine how the pharmacological profiles of these variants are modified by QC, we are currently repeating these experiments in CRISPR cells that are deficient in certain molecular chaperones of interest. Preliminary findings reveal that the spectrum of known CF variants exhibit a moderate attenuation of expression in cells lacking calnexin and a severe attenuation of expression in cells lacking the ER membrane protein complex. We are currently in the process of determining which variants are more- or less-sensitive to these QC proteins. Our results will reveal a broad overview of how QC interactions shape the pharmacological profile of rare CF variants and will pave the way for the targeting of forthcoming precision therapeutics.