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A yeast phenomic model for the gene interaction network modulating CFTR-ΔF508 protein biogenesis

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Abstract

Background: The overall influence of gene interaction in human disease is unknown. In cystic fibrosis (CF) a single allele of the cystic fibrosis transmembrane conductance regulator (CFTR-ΔF508) accounts for most of the disease. In cell models, CFTR-ΔF508 exhibits defective protein biogenesis and degradation rather than proper trafficking to the plasma membrane where CFTR normally functions. Numerous genes function in the biogenesis of CFTR and influence the fate of CFTR-ΔF508. However it is not known whether genetic variation in such genes contributes to disease severity in patients. Nor is there an easy way to study how numerous gene interactions involving CFTR-ΔF would manifest phenotypically.

Methods: To gain insight into the function and evolutionary conservation of a gene interaction network that regulates biogenesis of a misfolded ABC transporter, we employed yeast genetics to develop a 'phenomic' model, in which the CFTR-ΔF508-equivalent residue of a yeast homolog is mutated (Yor1-ΔF670), and where the genome is scanned quantitatively for interaction. We first confirmed that Yor1-ΔF undergoes protein misfolding and has reduced half-life, analogous to CFTR-ΔF. Gene interaction was then assessed quantitatively by growth curves for approximately 5,000 double mutants, based on alteration in the dose response to growth inhibition by oligomycin, a toxin extruded from the cell at the plasma membrane by Yor1.

Results: From a comparative genomic perspective, yeast gene interactions influencing Yor1-ΔF biogenesis were representative of human homologs previously found to modulate processing of CFTR-ΔF in mammalian cells. Additional evolutionarily conserved pathways were implicated by the study, and a ΔF-specific pro-biogenesis function of the recently discovered ER membrane complex (EMC) was evident from the yeast screen. This novel function was validated biochemically by siRNA of an EMC ortholog in a human cell line expressing CFTR-ΔF508. The precision and accuracy of quantitative high throughput cell array phenotyping (Q-HTCP), which captures tens of thousands of growth curves simultaneously, provided powerful resolution to measure gene interaction on a phenomic scale, based on discrete cell proliferation parameters.

Conclusion: We propose phenomic analysis of Yor1-ΔF as a model for investigating gene interaction networks that can modulate cystic fibrosis disease severity. Although the clinical relevance of the Yor1-ΔF gene interaction network for cystic fibrosis remains to be defined, the model appears to be informative with respect to human cell models of CFTR-ΔF. Moreover, the general strategy of yeast phenomics can be employed in a systematic manner

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