

Systems biology analyses of molecular networks in human tissues and misfolding diseases

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I. SUMMARY: The folding and secretory pathways comprising ER, Golgi system and plasma membrane are essential for both cell homeostasis and adaptation. Although the molecular species in these pathways are continuously being identified by molecular biology techniques and by genomics and proteomics technologies, the organizing principles of folding and trafficking pathways are poorly understood. Here we describe integrative approaches based on data mining and graph algorithms to analyze the interactions networks across human tissues and to identify active subnetworks and regulatory circuits that perform tissue specific functions. The study focuses on subnetworks that drive folding and secretory pathways in specific tissues, and whose malfunctions lead to conformational diseases.

II. ACTIVE NETWORKS in HUMAN TISSUES: In a first step, we build an atlas of *active subnetworks across human tissues*. An active subnetwork (module) represents connected regions of an interaction network that shows significant changes in expression over special sets of conditions (or tissues) [1].

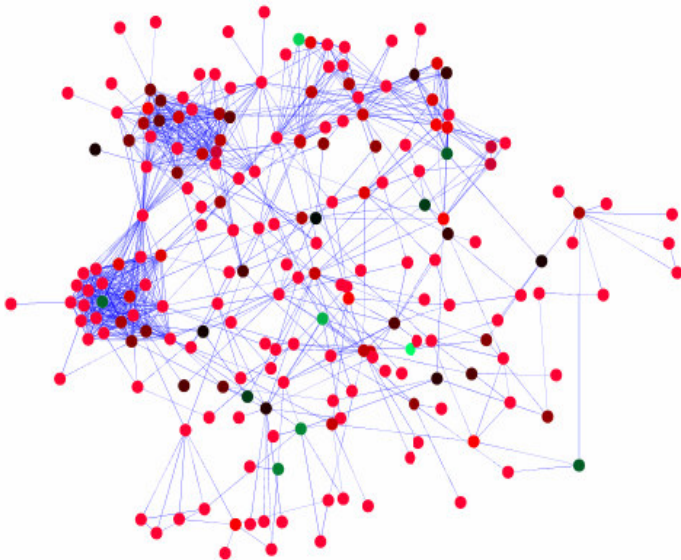


Figure 1: A potential active subnetwork in the bronchial epithelial cells (BEC). The module includes protein-protein interactions from HPRD, BIND, REACTOME databases. The color code indicates the degrees of significance of differential gene expression levels in BEC versus other tissues.

We use Cytoscape [2] to integrate an extended human protein-protein interaction network with the gene expression profiles available in SymAtlas for 79 human tissues [3]. The active subnetworks (modules) in distinct human tissues are identified using the

jActiveModule algorithm [1]: these modules may carry tissue-specific functions and confer distinct tissue identity. We compare and contrast the active subnetworks in different tissues, particularly in the tissues where unique mutations trigger major dysfunctions. Especially for cystic fibrosis, limited CFTR abundance leads to multiorgan disease, affecting the lung, pancreas, gut, liver, sweat glands and the reproductive organs.

III. ACTIVE NETWORKS in HUMAN DISEASES: In a second step, we aim to identify *active modules in pathological states*. We focus on a disease where genomics and proteomics offer the opportunity to examine global alterations in the mRNA and protein expression patterns. We study cystic fibrosis, an inherited lethal pulmonary disorder, where the $\Delta F508$ mutation in CFTR determines protein misfolding and degradation by proteasome, and multisystem disease. Multidimensional protein identification technology (MudPIT) was employed by our lab to identify CFTR interactions required for CFTR folding and trafficking [4], in normal and disease samples. We integrate the mass spectrometry data with the PPI networks and the gene expression profiles in normal and disease samples [10] in order to identify the active circuits that control CFTR biogenesis and function.

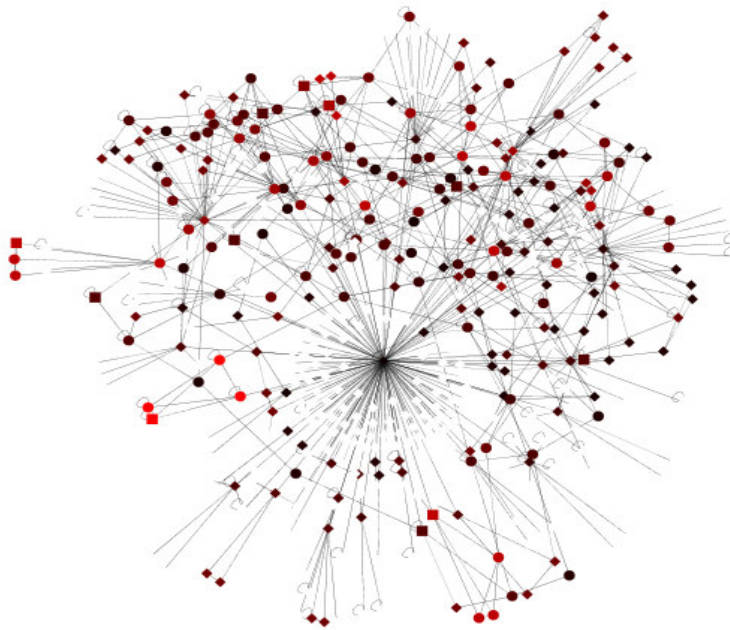


Figure 2: CFTR protein-protein interaction network. It was build using BioNetBuilder plugin [5] in Cytoscape [2] by integrating the MS data for the wild-type and mutant CFTR in BHK, Calu3, HT29, and T84 cells [5] with the human PPI data reported by public databases (HPRD, DIP, BIND) and by other studies [8,9]

Network analysis of $\Delta F508$ -CFTR, WT-CFTR and $\Delta F508$ /WT-CFTR interactomes revealed a scale-free and hierarchical topology. MCODE algorithms [6] were used to predict molecular complexes along CFTR trafficking pathways and to annotate new genes with a potential role in folding [7]. The new hypotheses will be addressed experimentally and the results could provide important insights and useful targets for intervention and therapy.

IV. REFERENCES:

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