208e Inferring Pathways That Confer a Cellular Phenotype by Integrating Gene Expression and Metabolic Profiles

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Cellular systems are controlled by interconnected signaling and regulatory networks. Elucidating the underlying pathways would facilitate the identification of therapeutic targets. Gene expressions, proteins and metabolites can be profiled for a cellular state. A systems approach can assist in the integration of these different high-throughput data to infer the underlying pathways. In this paper, a systems approach was developed to integrate gene expression and metabolic profiles to identify pathways related to a metabolic function. The approach first extracts features from the metabolite profiles to discriminate different phenotypes with linear (e.g. Fisher discriminant analysis (FDA), PCA) and non-linear methods (e.g. kernel FDA, kernel PCA); and then selects genes relevant to these features with genetic algorithm coupled partial least squares analysis and independent component analysis[1]; and finally reconstructs the pathways from the selected subset of genes using Bayesian network analysis [2].

We applied the approach to investigate the cytotoxcity related pathways in a human hepatoblastoma cell line (HepG2/C3A). In this cellular system, saturated fatty acid and acute TNF-alpha exposure were found to be cytotoxic, although chronic TNF-alpha exposure was found to be cytoprotective. Genes encoding biomolecules in pathways involved in regulating cytotoxicity were selected and the pathways were reconstructed. Several pathways were experimentally validated by perturbing the pathways and measuring their protein levels. Finally, the BN network analysis was applied to predict LDH release and the effects of perturbing genes, e.g. stearoyl-CoA desaturase and Bcl-2 on LDH release were simulated using the model. The results illustrate that the integration of gene expression and metabolite data by our framework provides informative and testable hypothesis on the mechanism(s) of palmitate-induced cytotoxicity.

Reference:

1. Li, Z. and C. Chan, Integrating gene expression and metabolic profiles. Journal of biological chemistry, 2004. 279(26): p. 27124-37.

2. Li, Z. and C. Chan, Inferring pathways and networks with a Bayesian framework. FASEB Journal, 2004. 18(6): p. 746-748, 10 1096/fj 03-0475fje.