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Channing Network Science Seminar

May 1, 2015, 11am @ 5th floor conference room

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IDEAL: Impact of Differential Expression Across Layers in multiple omics networks associated with asthma

Abstract: To understand the higher order regulation and the interplay that defines disease pathology, we require "NEW (Network-Enabled Wisdom) biology" for integrating genome-wide scale "omics" data. In particular, the functional understanding of the gene expression changes through non-coding RNAs in complex diseases like asthma remains unclear. Given their inherent pleiotropic actions to repress multiple gene targets simultaneously, microRNAs (miRNAs) could be useful in identifying the modules of co-regulated disease-associated genes and could be targeted to alter the functions of disease modules. We first noted that at the mRNA level, the differentially expressed genes (DEGs) form a significantly large connected component in the interactome, or a "disease module". This is consistent with the view that the disease process is caused by a set of disease-associated genes linked together by a network of interactions rather than by a single or a few isolated genes. Furthermore, we observed that the mRNAs targeted by miRNAs have central positions in the disease module: when removed, the cohesiveness of the module is lost, which is not the case for random attack. Following this observation, we developed IDEAL-Impact of Differential Expression Across Layers in multiple omics networks, a method to rank the miRNAs by the extent of their impact on the disease module. IDEALconsists of two steps. In step 1, IDEAL identifies miRNA-mRNA pairs that are significantly differentially expressed in an inverse relation and are predicted to interact. In step 2, IDEAL ranks the miRNAs that have the highest impact on the disease module based on network-topology. IDEAL iteratively repeats step 2 until the impact cannot be increased. This defines a subset of miRNAs that produces the largest fragmentation of the disease module. Interestingly, the top-ranking predictions are not the ones with highest fold-change, which differ drastically from usual approaches. Conversely, high fold-change miRNAs have very low impact on the disease module. Overall, our results suggest that in the disease state, a collective of miRNAs target specific mRNAs that are essential to form a significant connected component, or disease module. We applied IDEAL on mouse (BALB/c) model with miRNAs, mRNAs and protein expression data. We identified specific IDEAL miRNAs for Th1 acute, Th1 chronic, Th2 acute and Th2 chronic conditions. For example, mir-27b, mir372, mir-106b and mir-18a were highly rank miRNAs for the Th2 chronic condition.

hosted by Yang-Yu Liu