

MEETING ABSTRACT

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Differential coexpression network modules observed in human hepatocellular carcinoma progression

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Background

While an understanding of the human interactome is within attainable reach [1], an impending challenge is to uncover the condition-specific dynamics of the protein-protein interaction (PPI) network, especially those that coordinate with disease progression [2]. Differential coexpression analysis (DCA) [3,4] has recently emerged as an effective approach to address this issue, but such an effort has yet to be thoroughly tested.

Materials and methods

In this work, we explored the validity of extracting context-specific PPI subnetworks by analyzing the differential coexpression of interacting protein pairs. We first compared highly differentially coexpressed genes (“high-DC genes”) with highly differentially expressed genes (“high-DE genes”) in terms of their fit within a PPI-network analysis. Then, in a human PPI network overlaid with gene-gene differential correlation (DC) values calculated from the microarray gene expression dataset GSE6764, we sought high-DC subnetworks for each disease stage transition of hepatocellular carcinoma (HCC).

Results

The validity of integrating DCA with a PPI network was demonstrated in two lines of evidence. First, higher expression correlations were associated with PPI pairs than non-PPI pairs, and exceptionally high DC values were observed within part of the PPI pairs. Second, compared with the high-DE genes, high-DC genes were more enriched with HCC-related genes and were more condensed in the

reference network. Then, we extracted DC-PPI subnetworks for the four transitions over five HCC stages. All subnetworks turned out to be significantly enriched with HCC-related genes, HCV-targeted genes, and cancer genes. A comparison of the multiple transition-wise subnetworks gene by gene enabled us to identify the recurrent hub proteins, while comparing them edge by edge allowed us to identify protein pairs with constantly-changing relationships.

Conclusions

We demonstrated a differential coexpression workflow within the context of a human PPI reference network. As applied to a multi-stage HCC expression dataset, our approach has generated a set of differentially coexpressed genes and network modules with promising candidates for follow-up HCC investigation.

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