

Active Modules and Relevance Networks during the cell cycle in HeLa cells

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Introduction and Motivation

During cell cycle and division, eukaryotic cells usually activate a variety of processes such as DNA replication, chromosome segregation and cytokinesis. To contribute to the understanding of the dynamics of molecules during cell division, we used Active Modules Analysis (Segal et al., 2004) to analyze previously published microarray data (Whitfield et al., 2002) reporting gene expression profiles during HeLa cell cycle. Next, Relevance Networks Analysis (Butte et al., 2000) was used to evaluate the interaction between the molecules of module GeneDeck_cell_cycle.

Methodology

According Whitfield et al., 2002, the biological samples were obtained from synchronized HeLa cells (reference samples from asynchronous growing HeLa cells). The microarray data was obtained from Stanford Microarray Database. All the samples were classified in one of the cell cycle phases: G2, G2/M, M/G1, G1/S and S.

We gathered modules from KEGG, STKE, BioCarta, Gene Ontology and genes identified by Whitfield et al., 2002. Their dynamics during the cell cycle were analyzed with Active Module Analysis (Segal et al., 2004; Esteves et al., 2007), performed considering the five cell cycle stages (Figure 1).

For the Relevance Networks Analysis (adapted from Butte et al., 2000) of module GeneDeck_cell_cycle (Figure 2), interaction represents significant correlation between two variables (i.e. molecules). The normalization of the data and all the analyses were performed with maigesPack, a R package, implemented mainly by Esteves GH and submitted to Bioconductor, <http://www.bioconductor.org/>).

Results and Conclusions

The Active Module Analysis indicates which modules of genes may play an important role as the cell cycle progresses. It revealed many cancer related modules, together with metabolism related modules (Figure 1), such as cell_cycle, cytoskeleton, glicerolipid metabolism and G2 genes as defined by Whitfield et al., 2002. This approach is different from the one used by Whitfield et al., 2002, which investigated periodically expressed genes, given the fact it does not take into account the periodicity of the cycle.

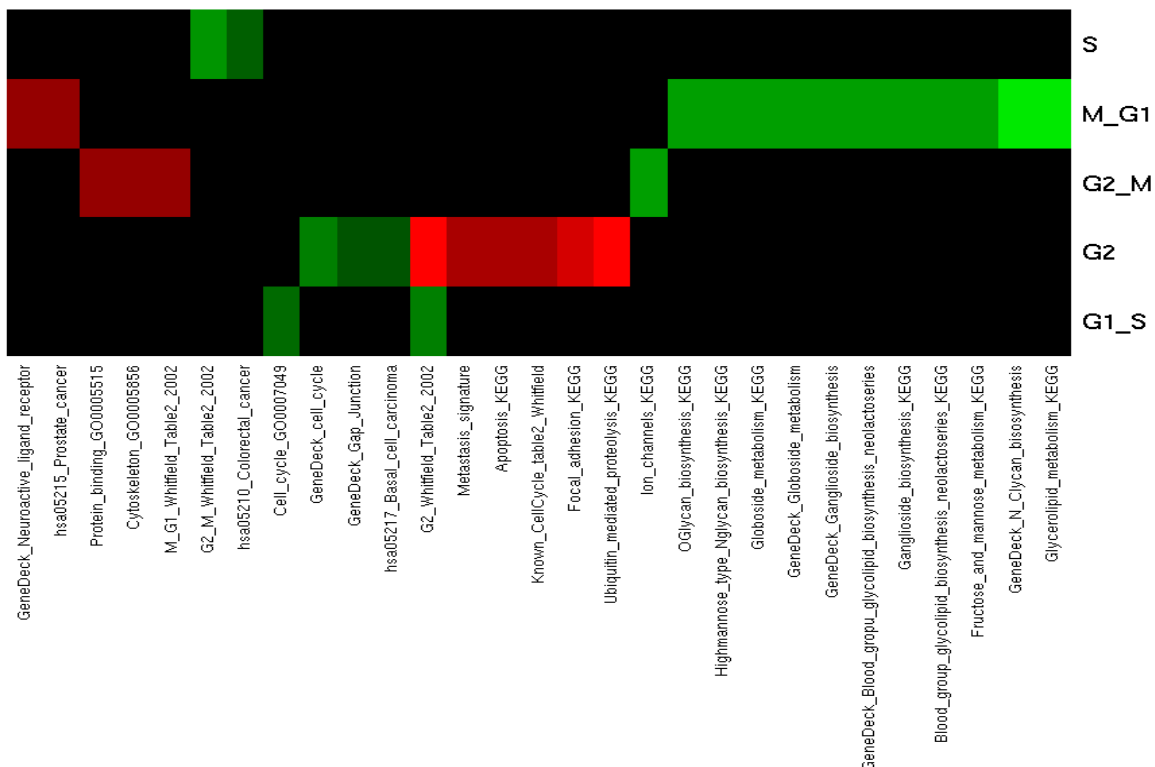


Figure 1: Active Modules for the five cell cycle stages: S, G2, G2/M, M/G1, G1_S.

The Relevance Networks Analysis provides a deeper inspection of the dynamics of GeneDeck_cell_cycle module. The first graph in Figure 2 shows the correlations between the genes present in that module for the G2 and G2/M phases. The second graph shows correlations between the genes for

the M/G1, G1/S and S phases and the third graph shows only significant changes between the correlations from graphs 1 and 2 (p-value < 0.00001). Interestingly, CCNA2 and CCND2 show very significantly changes for the correlations, probably due to their key roles in the cell cycle. In conclusion, these two analyses provided additional insights about biochemical processes occurring during cell cycle in HeLa cells, indicating cancer related modules and metabolic pathways, and also revealing the dynamics of molecules for module GeneDeck_cell_cycle.

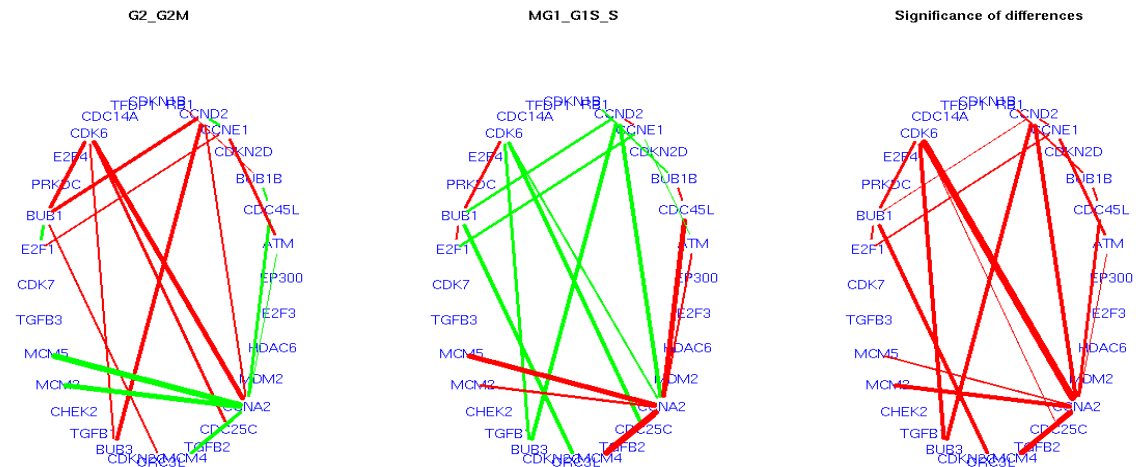


Figure 2: Relevance Networks for GeneDeck_cell_cycle module, for phases G2, G2/M versus M/G1, G1_S and S.

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