

# USING GENE REGULATORY NETWORKS TO STUDY GENE INTERACTIONS IN HUMAN LIVER CANCER

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The main objective of this study was to uncover interactions between genes by adopting a machine learning approach based on multiple expression measurements to represent these interactions. We used Bayesian networks to learn two gene networks from Microarrays experiments. Each network represented a different state of genes in a human liver tissue: non-tumor and Hepatocellular Carcinoma (HCC) tissues. We developed a system that constructs the networks based on a bayesian network learning algorithm, represents them graphically and provides a set of analytical functions for network comparison and analysis.

The data used in this study was taken from the work of Chen et al., 2002 This data represented gene expression in HCC and non-tumor liver tissues for a set of 3180 genes; 82 samples from HCC patients and 74 samples from non-tumor tissues. The total set of genes included different groups of genes, however, we were only interested in genes that had a role in cell proliferation, which was a subset of 94 genes.

Figure 1 shows a sub graph from the HCC network with edges suggesting a transformation mechanism. MYBL2 is v-myb myeloblastosis viral oncogene homolog. The protein encoded by this gene is a member of the MYB family of transcription factor genes involved in cell cycle progression. Searching for MYBL2 on the HCC network, it was found to have direct edges with two CDC's one of which is CDC2 that has been reported in literature to be activated by this transcription factor MYBL2. Subsequent nodes directly linked to the two CDC's were both members of the E2 ubiquitin-conjugating enzyme family and again both of them have edges to GPC3, member of cell surface heparan sulfate proteoglycan family. HCC cells have been shown to express GPC3 at high levels and it has been proposed that the modulation of growth factors by GPC3 may have a role in liver carcinogenesis. The consistency of MYBL2→CDC→UBE→GPC3 in the two branches of the diagram (given no prior knowledge given to the learning algorithm) suggests that there is a certain mechanism that affects the expression of GPC3. The edges between the CDK's and the Ubiquitin Conjugating Enzymes could be viewed as a temporal relationship as the activity of UBE2 is present at the end of Anaphase to polyubiquitate mitotic cyclin to exist the M phase. The edges from both UBE2's to GPC3 suggests that GPC3 is affected by the cell cycle genes possibly towards the end of M phase and as MYB2 continues to activate mitotic CDK's, GPC3 continues to be highly expressed in a proliferating hepatic cell.

In contrast, MYBL2 was found directly related to cyclin-dependent kinase inhibitor (CDKN3) in the non-tumor network, which provides a biologically sensible reason to the alteration of its activity in non-tumor vs. tumor states, Figure 2.

We were able to extract several other biologically sensible features from the resulting networks that were verified by published literature. Hence, we propose that other plausible hidden knowledge can be discovered by further analyzing the networks.

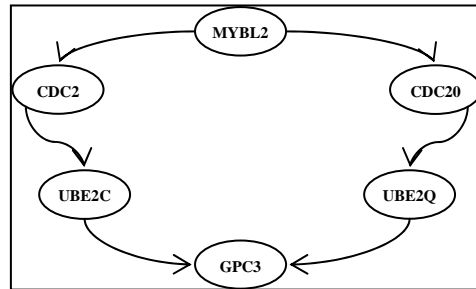


Figure 1. Edges suggesting a mechanism by which GPC3 becomes highly expressed in HCC tissues. This diagram suggests that GPC3 is affected by cell cycle genes and thus it is highly expressed in proliferating cells.

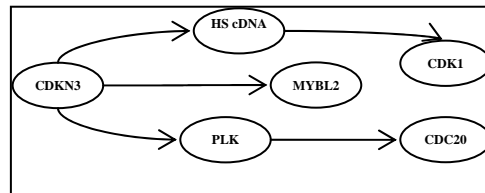


Figure 2. Edges in the non-tumor network suggesting common inhibition of mitotic CDK's and MYBL2 by a CDK inhibitor