Regulatory Signatures of Cancer Cell Lines Inferred from Expression Data

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While gene expression data is widely available describing mRNA levels in different cancer cells lines, the molecular regulatory mechanisms responsible for these changes are still poorly understood. Here we developed a rationale approach to infer regulatory mechanisms governing changes in gene expression by integrating datasets of protein/DNA interactions, protein-protein interactions and kinase-substrate interactions collected from prior biological knowledge. We first utilize data obtained from genome-wide ChIP-on-chip and ChIP-Seq experiments to connect mRNA expression levels of the NCI-60 cancer cell lines to the transcription factors most likely regulating them. These identified transcription factors are then "connected", using known protein-protein interactions, to form cancer specific sub-networks. Within these sub-networks we assess the enrichment for protein kinase substrates to infer the protein kinases likely regulating these complexes. Finally, using quantitative comparison of the up and down regulated genes for each cancer cell line, and genes affected by FDA approved drugs applied to cancer cells, we predict the mechanisms of action of these drugs. Following this path, from changes in gene expression to transcription factors to protein kinases we can provide a more thorough understanding of the regulatory mechanisms behind the observed mRNA levels in the NCI-60 cancer cell lines and other cancer cells. This approach proposes mechanisms of action for drugs. Wet lab experimental validation of this approach is still necessary, it can be done using single drugs or combinations of them.