Designing Gene Regulatory Networks for evaluating drug targets in lung cancer- A systems biology approach

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ABSTRACT

With the emergence of high throughput technologies in the post genomic era like DNA microarray, ChIP-chip, etc. have greatly aided our understanding towards cancer pathways and its treatment. Applications of Systems Biology to infer from these technologies have provided further insights to cancer progression.

In our present study we collected 148 microarray experimental data for four different types of Lung Cancers (Large Cell Lung Carcinoma, Squamous Cell Carcinoma, Adenocarcinoma and Small Cell Lung Carcinoma) during different stages of cancer progression and grouped them into three categories:- 1) Normal Vs Tumor, 2) Normal Vs Metastatic, 3) Tumor Vs Metastatic. We analyzed the expression profiles of different genes to identify outliers across different cell lines and compared it within the four cancer subtypes for consistencies by the application of fitness tests, to neglect false positives.

From the outcomes of the gene datasets, we generated and compiled the Gene Regulatory Networks (G.R.N.). Simultaneously, for each major common outlier, pathways were reconstructed. We analyzed these networks and compared them group wise for inferring a meaningful conclusion, which in this case can be very useful in evaluating new drug targets. We thus have correlated the gene expression levels of various genes in different stages of lung cancer progression and have evaluated potential target proteins for drug discovery in lung cancer.

This is novel Systems Biology approach in predicting new proteins for drug targets by analyzing global gene expression profiles of lung cancer subtypes.

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CANCER DRUG TARGET NETWORK

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ABSTRACT

In past decade, better understanding of the relationships between cancer drugs and their molecules target proteins have yielded many efficient small molecules for cancer treatment. We have analyzed ‘105’ existing anti-cancer drugs approved by the United States Food and Drug Administration (USFDA) in past 20 years for their efficiency, molecular mechanisms and the reasons for their success. We constructed a bipartite graph of these approved drugs and their target proteins linked together on the basis of drug-target associations. With the help of this network graph, we built a drug network and a target protein network. Simultaneously, with the same methodology we compared ‘105’ new molecular entity under late phase II and phase III of clinical trials or waiting for approval by USFDA. The topological analysis of these networks provided us with the highly interlinked giant components within the networks, their clustering coefficient and overall degree distribution.

Further, the target proteins for these drugs were located in a protein-protein interaction network of humans and the network was analyzed for various essential and non-essential proteins used as target proteins. On such basis we screened the cancer drugs working on the etiological aspect from the ones with palliative effect.

It has been observed that there is a need to focus on some new target proteins, which have not been the focus of many pharmaceutical companies, which might increase a drug’s efficacy in the treatment of cancer.