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Mapping of Natural Antimutagenic Chemotherapeutic Drug Targets on Colon Cancer Network using System Biology Approach

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Abstract

Recent studies have shown the evaluation and validation of cancer drugs and their targets. Even though the specificity of drug targets is a great challenge in the pharmaco-proteomics field of cancer biology [1]. To eradicate such hurdle, here we have taken a novel step to study the relation between drug target network and the corresponding drug network using the advanced concept of proteomics and network biology [19, 26, 27, 10]. The literature mining along with the OMIM database give the details of diseased genes which are further subjected to design a well connected gene regulatory network of cancer. The resultant network is then extrapolated to proteomics level to sort out the genes only expressed in the specific cancer types. The network is statistically analyzed and represented by the graphical interpretation to encounter the hub nodes and their locally parsed neighbors, ligand verses multi receptor docking and the propensity of drug targets in hub nodes and related subnetworks.

Keywords: Chemo preventive Drugs, Systems Biology, Ligand Interaction, gene regulatory network.

Introduction

Recent studies have shown that drug treatments are becoming very much pronounced in genetic diseases encountering the disease genes in the proteomics level [2, 3,8]. Even the identification of the specific oncogenes andtumor suppressor genes related to Colon cancer has taken up many challenges [4]. But there lies a great complexity among the genetic interactions of the cancer disease genes which still not fully recovered. Cancer usually is the cause of the altered interaction between the multiple

genes rather than changes in a single causal gene [5]. And the functional interactions predict the priority of the highly connected nodes and its neighbors [6,11, 12]. But to study the target specificity of small molecules on the Colon cancer genes, the expression level study is much essential [13,16]. As post transcriptional modification plays a crucial role in the gene expression [13]. So the genes highly expressed in the Colon cancer are sorted out for the further experimentation. This result is subjected to design a well connected network system to define the biological behavior. The degree distribution of the nodes defines its importance and biological hierarchy [6, 9]. To study the effects of Colon cancer specific ligands on the biological network of Colon cancer, here a novel method has been used which applies the surjective function to demonstrate the drug-target relations.

For the validation of the result, one ligand versus multi receptor docking has been performed to elucidate the high specificity of the ligands for best fit. This analysis has been done on the basis of their docking score and RMS value. Hence here a structural classification has taken place for the interpretation of system biology network model.

Methodology

Constructing Colon Cancer Gene Regulatory Network

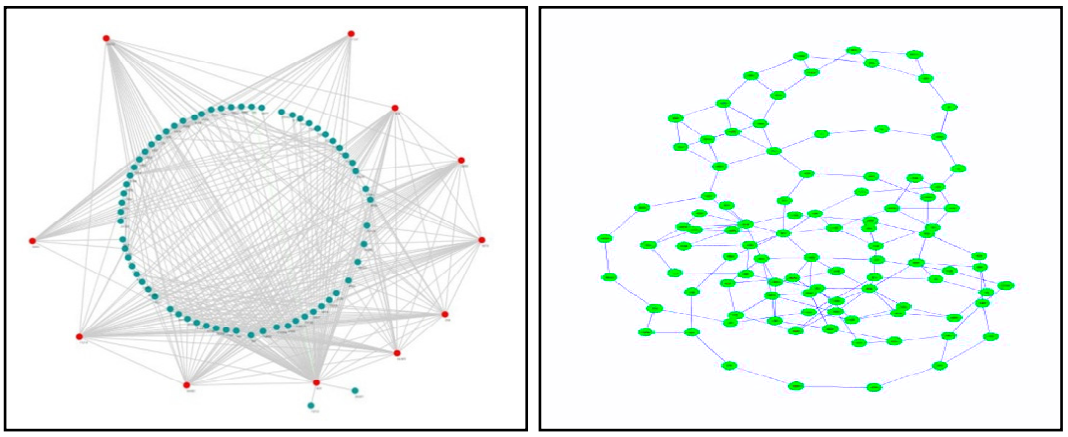
Cancer genes usually contain information about genes which are targets for cancer-causing mutations; proto-oncogenes and tumor suppressor genes. The Colon cancer related genes are extracted from the OMIM database ignoring the pseudo genes by the query search method [18]. They are then subjected to the expression profiling to get the protein coding genes. Microarray data are collected from the public database of the NIH Gene Expression Omnibus. Out of 81 genes, only 11 genes show high connectivity and prominence in the network system. [Supplementary file 1]. The essential nodes with high interactions are subjected to the statistical analysis to evaluate the data. [Shown in Table 1].

Table 1: Showing the graph property of the highly interacting Nodes.

Degree Centrality	Betweenness Centrality	Closeness Centrality			
Molecule	Score	Molecule	Score	Molecule	Score
BCL6	1	BCL6	0.733	BCL6	1
AKAP13	0.442	AKAP13	0.037	AKAP13	0.642
RHOU	0.364	NCOA3	0.026	RHOU	0.611
RHOQ	0.364	TP53	0.014	RHOQ	0.611
RHOH	0.364	ESR1	0.008	RHOH	0.611
RHOF	0.364	BRCA2	0.008	RHOF	0.611
RAC2	0.364	RHOU	0.007	RAC2	0.611
RAC1	0.364	RHOQ	0.007	RAC1	0.611
ARHGAP4	0.364	RHOH	0.007	ARHGAP4	0.611
NCOA3	0.286	RHOF	0.007	NCOA3	0.583

The Hub genes and their neighbor genes are uploaded into the Cytoscape, the cellular network analyzer software to get the visualization of the entire network. Here the Cytoscape version 2.6 has been used with other plugins.

The graphical view of the network has been taken which gives the priority of the hub nodes beside other locally parsed nodes. For further validation of the drugs those nodes are given more focus than other neighbors with low degree distribution.



a **b**

Figure 1a: Showing the Colon cancer gene network with the highly connected Hub nodes (red in color). **1b:** Showing the random interaction among the nodes in Colon cancer network.

Construction of Ligand Network

The Colon cancer specific natural antimutagens were annotated from a wide range of publishers and databases like Wiley, Blackwell Synergy, Medline, Pubchem, Ingenta Connect, Chemfinder, Drug Bank etc. To find the interaction between the small molecules on the basis of their receptor specificity, the ligand network has been designed in Cytoscape using Metascape Plugin. The network shows the scale free property like other biological networks illustrating that some small molecules are more linked to many reactions while others behave just as a discrete node of those highly connected nodes. The resultant network has been shown in the Fig 2. Now to validate the target specificity both the network is being co-related. The ligands are subjected to multi receptor docking. The docking score and RMS value here defines how well the ligand having target flexibility with the particular receptor. On the basis of the score the mapping is done on the Colon cancer network consisted of Colon cancer receptor protein. According to Park K & Kim D, the ligand and binding sites are associated with protein functions [7]. So a good docking score prove a ligand to be ideal for drug target.

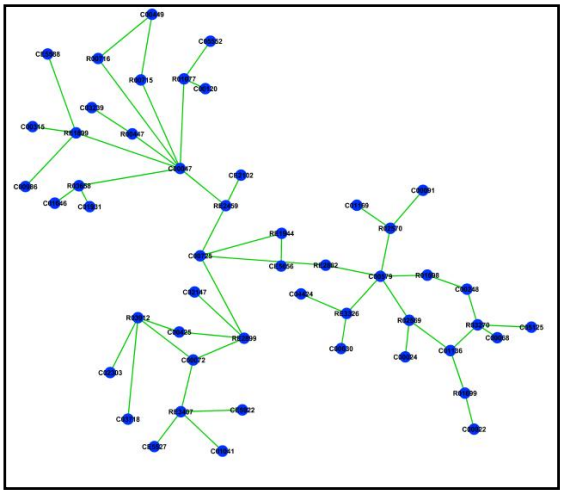


Figure 2: Showing the interaction between the small molecules on the basis of their receptor specificity.

Statistical Analysis

The two sets (X, Y) of ligands and the target receptors respectively are taken and formulated with the Surjective Function which says that for every y in the codomain Y there is at least one x in the domain X such that $f(x) = y$. In the Figure 3, it has been shown that the way a ligand interact with receptors. Again for the reverse analysis, the target set also shows the mode of interaction which can be well explained by this statistical and mathematical function.

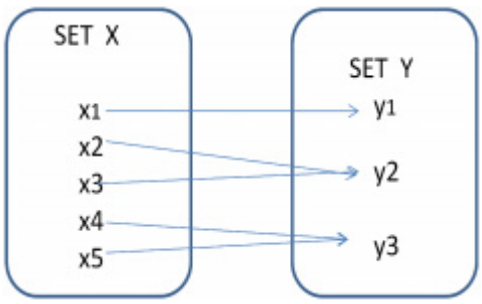


Figure 3: showing the mode of interaction among the ligand set and the target set using Surjective Function where set X is the ligand set and set Y is the target set.

So each Colon cancer specific ligands when multi targeted with these nodes gives optimum results than other neighbors which are not so interactive in the network graph. Even among this the two most prominent tumor suppressor gene BRCA2; BRCA1 shows maximum target specificity indicating that Colon cancer specific drugs are specific for the particular disease gene and not random among the networks. The graph showing on Figure 3a and 3b indicates that Acacetin is having high docking

score with BRAC1 and BRAC2 where as Ferulic acid is having high score only with ANKRD17 ignoring the rest of the Hub nodes. The graphical representation [Supplementary file 3] shows the specific propensity of drug targets. Thus it is been concluded that these disease genes are much prone to be act upon by

Result and Analysis

The interpretation of the Colon cancer network gives 11 Hub nodes viz: BRCA 2;BRCA1; NCOA6; NCOA3; MRPS26; ANKRD17; SEPTIN 1; FBXO31; TRERF1; RHOBTB2; AKAP13. Here due to huge number of interactions among 81 Colon cancer genes the threshold of degree distribution has been set to ≥ 10. So in the hierarchy order of the degree distribution the nodes are taken into considerations which are having highest order of degree distribution. [Supplementary file 2] So each Colon cancer specific ligands when multi targeted with these nodes gives optimum results than other neighbors which are not so interactive in the network graph. Even among this the two most prominent tumor suppressor gene BRCA2; BRCA1 shows maximum target specificity indicating that Colon cancer specific drugs are specific for the particular disease gene and not random among the networks. The graph showing on Figure 3a and 3b indicates that Acacetin is having high docking score with BRAC1 and BRAC2 where as Ferulic acid is having high score only with ANKRD17 ignoring the rest of the Hub nodes. The graphical representation [Supplementary file 3] shows the specific propensity of drug targets. Thus it is been concluded that these disease genes are much prone to be act upon by the ligand. The network visualization makes the task more accessible to get an overview of the interactions of cancer genes. The statistical analysis of the sets of Ligand and receptor shows a Surjective Function as every ligand(x) taken as the element of the set of Ligand(X) is having relation with the element in the set of receptor (Y).

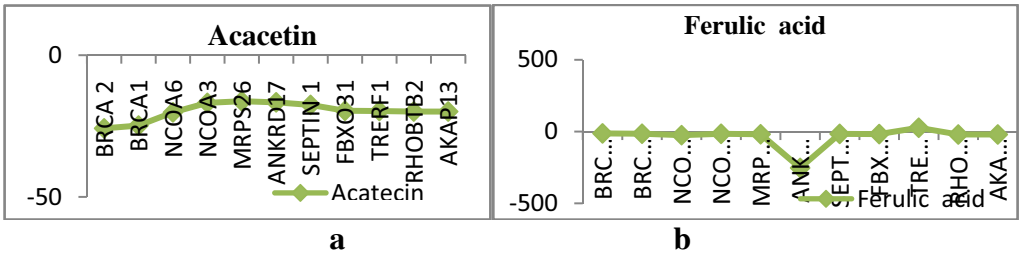


Figure 4a showing the target specificity of Acacetin with the Hub nodes depending on the docking score. **4b** showing the specificity of ligand Ferulic acid.

Significance and Conclusion

This review has demonstrated that there are some particular small molecules which response in specific cancer diseases. The specificity is not random. The analysis on the basis of graphical representation and network view has made the interpretation more lucid. The field of cancer biology is lacking with a strong database which would

put up the medical science with the small details of the chemopreventive drugs and specific cancer relativity. This review is the step forward to illustrate the drug targets of cancer biology with the aid of system biology.

Acknowledgements

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