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Mapping of natural antimutagenic chemotherapeutic drug targets on breast 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. The literature mining along with the OMIM database gives the details of diseased genes which are further subjected to design a well connected gene regulatory network of cancer. The network is statistically analyzed and represented by the graphical interpretation to encounter the hub nodes and their locally parsed neighbors. The ligand verses multi receptor docking and the propensity of drug targets in hub nodes and related sub-networks were further statistically examined in this study.**

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

I. INTRODUCTION

Recent studies have shown that drug treatments are becoming very much pronounced in genetic diseases thereby encountering the disease genes in the proteomics level has become more difficult [2, 3, 8]. Even the identification of the specific oncogenes and tumor suppressor genes related to breast 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 demystified.

This result is subjected to design a well connected network systems to define the biological behavior. The degree distribution of the nodes defines its importance and biological hierarchy [6, 9]. To study the effects of breast cancer specific ligands on the biological network of breast cancer, here a novel method has been used which applies the Surjective Function to demonstrate the drug-target relationship. 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.

II. METHODOLGY

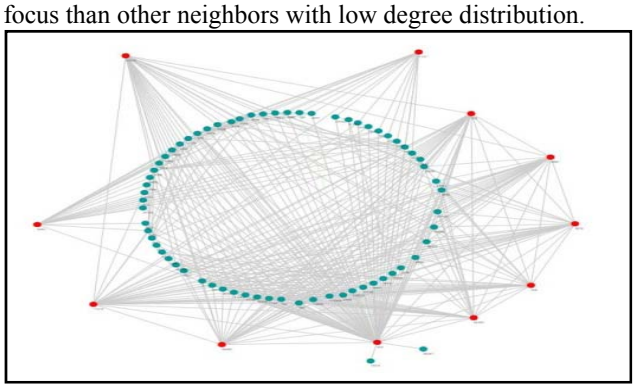
A. .Constructing Breast Cancer Gene Regulatory Network

Cancer genes usually contain information about genes which are targets for cancer-causing mutations; proto-oncogenes and tumor suppressor genes. The breast 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 I].

TABLE I. 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

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.



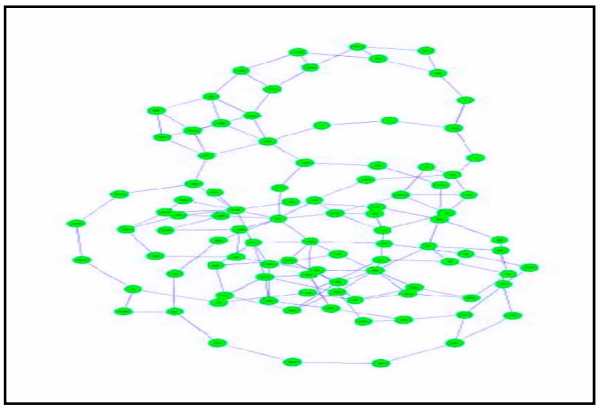


Figure 1a: Showing the breast cancer gene network with the highly connected Hub nodes (red in color).

Figure 1b: Showing the random interaction among the nodes in Breast cancer network.

III. CONSTRUCTION OF LIGAND NETWORK

The breast 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 using Quantum 3.3.0. 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 breast cancer network consisted of breast 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 indicates a ligand to be ideally fit for a drug target.

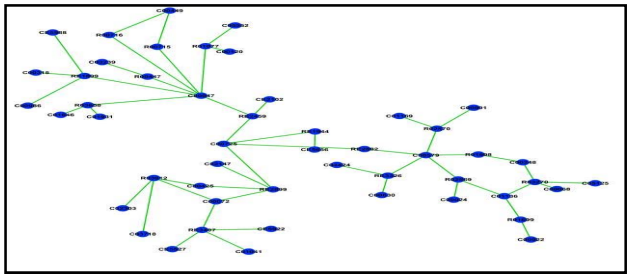


Figure 2: Showing the interaction between the small molecules on the basis of their receptor specificity.

The ligand ID has taken from the KEGG Ligand database.

IV. 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.

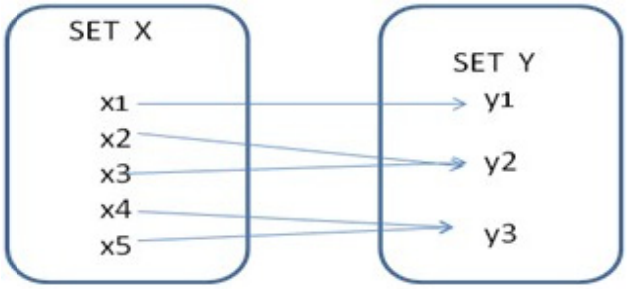


Figure 3: showing the mode of interaction among the ligand set and the target set using Surjective Function where set X is the ligand set and set Y is the target set.

V. RESULT AND ANALYSIS

The interpretation of the breast cancer network gives eleven Hub nodes viz: BRCA2; BRCA1; NCOA6; NCOA3; MRPS26; ANKRD17; SEPTIN 1; FBXO31; TRERF1; RHOBTB2; AKAP13. Here due to huge number of interactions among 81 breast 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 breast 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 breast 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 BRCA1 and BRCA2 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 show 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).

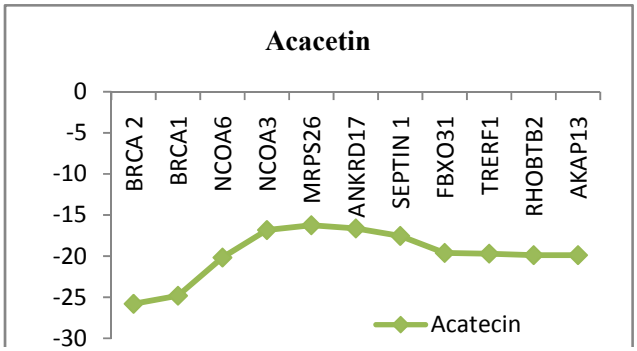


Figure 4a Showing the target specificity of Acacetin with the Hub nodes depending on the docking score.

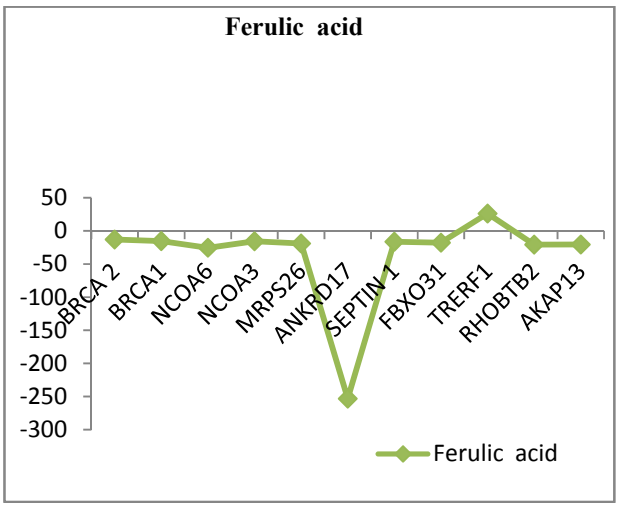


Figure 4b Showing the specificity of ligand Ferulic acid.

VI. 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. Though the data of full cancer network is far from complete, still the study gives a statistical review of how the drug trends will be coming into the cancer biology field.

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