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RESEARCH ARTICLE

MAPPING OF NATURAL MMP INHIBITOR TARGETS ON LUNG CANCER NETWORK USING SYSTEMS BIOLOGY APPROACH

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ABSTRACT

Identification of protein-ligand interaction networks on a proteome scale is crucial to address a wide range of biological problems such as correlating molecular functions to physiological processes and designing safe and efficient therapeutics. In this study we have developed a novel computational strategy to identify ligand binding profiles of proteins across gene families and applied it to predicting protein functions, elucidating molecular mechanisms of drug adverse effects, and repositioning safe pharmaceuticals to treat different diseases 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. The objective of developing a biological networking is for the evaluation and validation of cancer drugs and their targets. In the field of cancer biology, the drug and their targets holds a role of paramount importance. With the work conducted here it shows the study of relation between drug target networks. Lung cancer is one of the main types of cancer in which the lung tissues are affected

Genes belonging to the group of proto-oncogenes and tumor suppressors are best targeted for cancer studies. Biological networks like gene regulatory networks, protein interaction network is usually created to simplify the studies. The genes were collected from OMIM database for the lung cancer, respective targets were found using PDB and Gene Cards using the VisANT the biological networks has been drawn. From the literature study about 40 metalloproteinase inhibitors were collected and out of those 12 molecules show anticancer activity against lung cancer. The flexible docking has been performed for Target Protein Vs 12 compounds, Using the best docking score, the graphs obtained from the docking analysis is statistically validated with the help of VisANT. The compound with best docking score were subjected to ADMETOX through which it drawn out the potential candidate using ADME/TOX WEB. Thus out of 12 natural molecules one molecule was selected namely Eicosapentaenoic Acid where it showed the best docking score as well as average ADME property.

INTRODUCTION

The protein and ligand interaction takes an important part in protein function. Both ligand and its binding site are essential components for understanding how the protein-ligand complex functions. Until now, there have been many studies about protein function and evolution, but they usually lacked ligand information. Accordingly, in this study, we tried to answer the following questions: how much ligand and binding site are associated with protein function, and how ligands themselves are related to each other in terms of binding site and proteins with highest interaction.

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Through the network analysis, we attempted to reveal systematic relationship between the ligand and protein network (Kontogiorgis, *2005*). There are a myriad of problems which make successful treatment of cancer difficult. Most cancers are highly invasive and there are problems of recurrence even after surgery, chemotherapy and radiation treatment. MMPs are a family of highly homologous metal dependent endopeptidases that can cleave most of the constituents of the extracellular matrix such as collagen, fibronectin, laminin and elastin (Ohba, *1995*) and are inhibited by endogenous tissue inhibitor of metalloproteinases (TIMPs) or synthetic inhibitors such as EDTA and phenanthroline. The ratio of activated MMPs and TIMPs is a key determining factor

between degradation and biosynthesis of the matrix.Matrix metalloproteases have been particularly implicated in tumor invasion and angiogenesis. Comprehension of the exact mechanisms involved in MMP activity has been complicated by the differing expression patterns and roles of these proteases within the tumor (Maria Pavlaki, 2005). Further complicating the situation, these enzymes have overlapping substrate specificities (Naghma Khan,2006) creating difficulty in designing appropriate inhibitors for only one protease (Keiji Inoue, 2002). In addition, the MMPs are present at globally low concentration, but they are concentrated on the surface of cells at highly elevated and activated concentrations.

Recent studies have shown that drug treatments are becoming very much pronounced in genetic diseases encountering the disease genes in the proteomics level (Papaioannou, 2005, Goto, 2005, XU Tian-Min, 2008). Even the identification of the specific oncogenes and tumor suppressor genes related to breast cancer has taken up many challenges (Ferdinando Mannello,2 006). 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 (Pavlaki Maria, 2003). And the functional interactions predict the priority of the highly connected nodes and its neighbors (Naghma Khan, 2006; Woochang Hwang, 2006). But to study the target specificity of small natural MMP Inhibitors on the lung cancer genes, the expression level study is much essential. As post transcriptional modification plays a crucial role in the gene expression .So the genes highly expressed in the lung cancer are sorted out for the further experimentation. 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 (Hui, 1998). To study the effects of lung cancer specific MMP Inhibitors on the biological network of lung cancer, 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. The lung cancer specific natural MMP Inhibitors 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 VizANT. 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.

MATERIALS AND METHODS

A. Data mining, Target and Lead Identification

The initial step carried out here is collection of genes. In OMIM database the disease gene were collected to study the particular types of cancer. The lung cancer specific natural MMP Inhibitors were annotated from a wide range of publishers and databases like Wiley, Blackwell Synergy, Medline, Pubchem, Ingenta Connect, Chemfinder, Drug Bank etc. The protein complex structures were collected from various online databases. The complex protein and the small molecules were collected from various sources and these were subjected to multi-receptor docking analysis using Quantum 3.3.0., After the protein and ligand docking the matrix has been created for the scores obtained. From the score the target and the lead were identified.

B. Binding Site Analysis

Identification and evaluation of surface binding-pockets and occluded cavities are initial steps in protein structure-based drug design. Characterizing the active site's shape as well as the distribution of surrounding residues plays an important role for a variety of applications such as automated ligand docking or *in situ* modeling. After the multi receptor docking step, the protein and the MMP inhibitor was subjected to binding site analysis in Q site Finder.

C. Sequence and Evolutionary Analysis

The sequence analysis was done for the MMP target proteins for lung cancer (MMP2, MMP9, MMP10, MMP28) (Joe Felsenstein, 1993). The sequence analysis score shows a fair results of 30 – 40 % (Fig. 2) the evolutionary tree was drawn using PHYLIP 3.69 [*http://vizant.sourceforge.net/]*. A rooted phylogenetic tree with a unique node corresponding to the most recent common ancestor was found using the evolutionary analysis study (Fig. 3).

Table1. MMP (2,9, and 10) shows the sequence analys is score circled in red

SeqA	Name	Len(nt)	SeqB	Name	Len(nt)	Score
1	2	3402	2	9	2387	32
1	2	3402	3	10	1743	15
1	2	3402	4	28	1753	4
2	9	2387	3	10	1743	13
2	9	2387	4	28	1753	10
3	10	1743	4	28	1753	5

Table 2. List of natural MMP inhibitors taken for the study

		2A20	1WHN	3BIN
Curcumin	-23.22	-15.61	-22.77	-25.49
Diadzein	-16.66	-18.33	-23.59	-18.16
EPA	-19.39	-21.84	-30.06	-23.57
Genistein	-17.34	-18.17	-24.46	-20.66
Kaempferol	-16.3	-17.96	-21.6	-19.11
Myricetin	-14.71	-17.66	-25.34	-18.65
Oleic Acid	-26.34	-20.49	-19.8	-15.66
Quercetin	-23.04	-20.42	-25.45	-25.15
Resveratrol	-17.73	-22.61	-12.9	-18.17
Delphinidin	-17.8	-16.18	-20.34	-18.86

Fig 2. MMP (2,9,and 10) shows the sequenceanalys is score circled in red

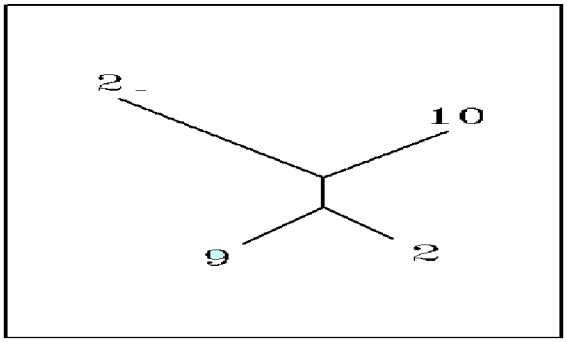

Fig 3. MMP (2,9,and 10) shows evolutionary relationship between the three MMPs

Statistical analysis

The two sets (X,Y) of ligands and the target receptors respectively are taken and using their mean docking score, the VizANT and the highest degree of interaction was found to be GNB2L1 (Fig. 4) gene, where it shares the both in-degree and out degree distribution and it was found to be average score of 1.378, and the correlation coefficient was found to be 0.77

RESULTS AND DISCUSSION

A. Network analysis

The highest interaction was found to be the GNB2L1 gene and the highest interaction was found to be with the MMP inhibitor EPA, found in fish oil.
[*http://www.healingcancernaturally.com/malignant-fibroushistiocytoma.html*].

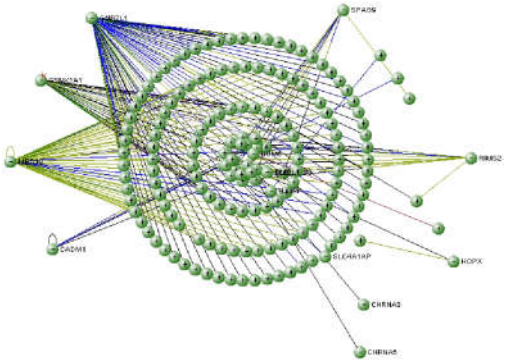

Fig 4. Highest interaction gene shown in blue color

Conclusion

The interpretation of lung cancer network gives 7 hub nodes. The most prominent interaction was observed in GNB2L1.Each specific MMP inhibitors were made to multi receptor docking. The highest docking score obtained was -22.63 K/cal. The MMP inhibitor EPA shows highest interaction with PDB ID 3BIN, (GNB2L1) when compared with the 12 other natural MMP inhibitors. ADME analysis proves the MMP inhibitor shows the less mutagenic activity. In this research work we conclude that the EPA (Eicosapentaenoic Acid) which shows the highest interaction with the protein 3BIN (PDB id).

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