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Original Research Article

Integrative analysis of protein-protein interaction networks: linking cellular functions to cancer and diabetes mechanisms

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ABSTRACT

Background: Protein-protein interactions (PPIs) are vital in regulating cellular functions, including signal transduction, metabolic control, and intracellular transport. In diseases such as diabetes and cancer, analyzing PPI networks provides valuable insights into underlying molecular mechanisms and potential therapeutic targets. Focusing on disease-specific subnetworks enables the identification of key proteins and their functional relationships.
Methods: A subset of the human PPI network associated with diabetes and cancer was analyzed to identify proteins involved in signaling, trafficking, and metabolism. Proteins such as ARF5, M6PR, FKBP4, CYP26B1, NDUFAF7, and FUCA2 were included in the dataset annotations. We utilized visualization techniques to generate PPI (protein-protein interaction) maps, isolate diabetes modules with key genes like INS, GCK, IGF1, PPARG, and GLUT4, and investigate their relationships with different cancer types using the adjusted p-value threshold.
Results: In this study, each protein contributed a unique aspect and function to the overall analysis. M6PR regulated the transport of lysosomal enzymes, while ARF5 played a role in Golgi-associated vesicle trafficking. Hormone receptor microtubule FCBP4, along with hormone-receptor microtubule dynamics, was involved in retinoic acid metabolism and germ cell development. NDUFAF7 played a crucial role in mitochondrial complex I assembly, while FUCA2 participated in glycoprotein catabolism. Furthermore, the diabetes-specific interaction modules revealed a core regulatory axis, which comprised INS, GCK, IGF1, PPARG, and GLUT4. These genes are significant insulin signaling and glucose metabolism genes. Beside that, notable associations were observed with endometrial, melanoma, and colorectal cancers.
Conclusions: Recording the interplay of metabolic pathways underscores the importance of ppi subnetworks in metabolic regulation, signal transduction, and associated disorders, which supports further drug target investigations in diabetes and cancer.

Keywords: Protein-protein interaction network, Diabetes, Insulin signaling, ARF5, M6PR, FKBP4, CYP26B1, NDUFAF7, FUCA2

INTRODUCTION

Protein-protein interactions (PPIs) are indispensable for physiological activities, counting communication, metabolism, and immune response, and gene regulation.[1] Mapping the human interactome reveals how these interactions preserve cellular homeostasis and how their disturbance causes disorders including cancer and diabetes.[2] Detailed PPI networks built using high-throughput technology and bioinformatics have exposed important functional modules and possible pharmaceutical targets.[3] While type 2 diabetes is branded by compromised insulin signaling and glucose metabolism, cancer is identified by altered protein signaling and uncontrolled

cell proliferation.[4] Through the analysis of PPI networks, the shared and distinct biological pathways of both diseases can be identified, highlighting possible interactions and streamlining treatment.

In this era of systems biology and precision medicine, this type of research is invaluable. PPI networks address the limitations of fragmented protein function research and provide a holistic view of molecular interactions in cells. Although mapping functional modules of PPI networks is essential in understanding how proteins collaborate to regulate crucial cellular functions, it has significant implications in identifying therapeutic targets and disease-specific biomarkers.[5] The inclusive strategy used here provides a useful tool for finding overlapping processes in cancer and diabetes by closing the gap across molecular biology and clinical application. Improving diagnosis accuracy and customizing treatment plans depend on such revelations.[6] To carry out an integrated investigation of PPI networks to find and describe important functional proteins connected to cancer and diabetes, so clarifying their functions in disease-specific and overlapping molecular pathways.

METHODS

This study employed an integrative systems biology method to investigate the functional significance of PPIs inside the contexts of cancer and diabetes. This study, conducted at [Department of Pharmacy, Jagdishprasad Jhabarmal Tibrewala University, Rajasthan] between time period (October 2024 to June 2025), employed an integrative systems biology approach to investigate the functional significance of PPIs within the contexts of cancer and diabetes.

Focusing on those with known or expected participation in oncogenic signaling and metabolic control, a curated list of human proteins was obtained from public protein databases like STRING and BioGRID. Based on biological relevance and annotation richness, a selection of six representative proteins e.g., ARF5, M6PR, FKBP4, CYP26B1, NDUFAF7, and FUCA2 was chosen from gathered protein identifiers and functional annotations. Using Cytoscape, protein-protein interaction networks were built and examined for topological characteristics like degree centrality, clustering coefficient, and acrossness. Using pathway analysis tools such as DAVID and KEGG, functional enrichment was carried out to find notable links with disease pathways. Separate subnetworks were built to concentrate on cancer-related (e.g., melanoma, glioma, lung, and endometrial cancer) and diabetes-related (e.g., INS, GCK, IGF1, PPARG, GLUT4) protein sets. Adjusted p-values (p.adjust) and interaction density plots helped to visualize the importance of pathway-disease correlations.

This network-based approach provided insight into possible therapeutic targets and molecular mechanisms by allowing the discovery of important regulatory hubs, interaction patterns, and biological procedures linked to the pathophysiology of cancer and diabetes.

RESULTS

An integrated examination of the PPI network spotted a functionally diversified group of proteins engaged in essential biological processes such as vesicle trafficking, metabolic control, enzyme activity, and signal transmission. With the proteins-ARF5, M6PR, FKBP4, CYP26B1, NDUFAF7, and FUCA2—each demonstrating its own cellular homeostasis-related function, the network seemed to have a more focused purpose. Its disease-specific interactions brought the most attention to visualizations. There was noticeable enrichment in several cancer types, including melanoma, endometrial cancer, and glioma, as well as in metabolic pathways relevant to diabetes, such as insulin signaling and glucose metabolism. While the diabetes-specific network subset clarified relationships across important metabolic proteins including INS, GCK, PPARG, IGF1, and GLUT4, the p.adjust-based dot plot underlined the various levels of statistical significance among several cancer types.

The identified fraction of proteins in the protein-protein interaction network plays various and important functions in cellular function, including in protein trafficking, signaling, metabolic control, and enzymatic activity. ARF5 (ADP-ribosylation factor 5) is a GTP binding protein involved in vesicular transport. It serves as an allosteric activator of the cholera toxin catalytic subunit. By recognizing phosphomannosyl residues, the mannose-6-phosphate receptor (M6PR) is responsible for the transport of lysosomal enzymes, ensuring their selective delivery into the endomembrane system. A peptidyl-prolyl cis-trans isomerase, FKBP4 helps to fold proteins, create hormone receptor complexes, and control microtubules, hence suggesting it in neuronal development and intracellular transport.

Reflecting its participation in differentiation and morphogenic signaling, the cytochrome P450 enzyme CYP26B1 is crucial in retinoic acid metabolism and germ cell development. Proper assembly of respiratory chain complex I depends on NDUFAF7, a mitochondrial arginine methyltransferase, therefore highlighting its importance in mitochondrial bioenergetics. Finally, an alpha-L-fucosidase named FUCA2 participates in the processing and turnover of glycans by removing fucose residues from glycoproteins.

Collectively, these proteins reflect a functional cross-section of several critical biological processes-such as vesicular transport, signal transduction, metabolic enzymes, and mitochondrial functions-thus informing hypotheses on their roles in health and diseases. Offering a comparison of which malignancies show greater molecular correlations, Figure 1 visually depicts the statistical significance (adjusted p values) of various cancer types in reference to certain protein activities.

Table 1: PPI network details.

Protein external_id	Preferred name	Protein size	annotation
<chr>	<chr>	<int>	<chr>
9606.ENSP00000000233	ARF5	180	ADP-ribosylation factor 5; a GTP-binding protein that acts as of cholera toxin's catalytic component's allosteric activator, which is an ADP-ribosyltransferase. Engaged inside protein trafficking; may regulate vesicle budding along with uncoating inside Golgi apparatus; ARF GTPase family
9606.ENSP00000000412	M6PR	277	Cation-dependent mannose-6-phosphate receptor; Phosphorylated lysosomal enzymes' transport from Golgi apparatus along with cell membrane to lysosomes. Lysosomal enzymes with phosphomannosyl residues particularly bind right to mannose-6-phosphate receptors inside Golgi apparatus, along with resultant receptor-ligand complex is then transported to an acidic prelysosomal compartment, wherein low pH facilitates complex
9606.ENSP00000001008	FKBP4	459	Peptidyl-prolyl cis-trans isomerase FKBP4; Immunophilin protein with PPIase along with co-chaperone activities. Component of steroid receptors heterocomplexes through interaction with heat-shock protein 90 (HSP90). May facilitate intracellular transport of heterooligomeric steroid hormone receptor types across cytoplasmic along with nuclear compartments. The isomerase activity regulates neuronal growth cones via modulating opening of TRPC1 channel. Functions as a regulator of microtubule dynamics by reducing capacity of MAPT/TAU to facilitate microtubule assembly. May provide a protective function.
9606.ENSP00000001146	CYP26B1	512	Cytochrome P450 26B1; Participates in retinoic acid (RA) metabolism, which involves inactivating this classical morphogen by oxidation. Participates in the selective inactivation of all-trans-retinoic acid (all-trans-RA), an action that establishes all-trans-retinoic acid > 9-cis-retinoic acid > 13-cis-retinoic acid as the order of substrates preference. Generates different RA hydroxylated metabolites, such as 4-OH-RA, 4-oxo-RA, and 18-OH-RA. Essential for postnatal survival. By inhibiting STRA8 expression and thus delaying meiosis, plays an essential role in germ cell development by degrading retinoic acid in the developing testis. Required [...]
9606.ENSP00000002125	NDUFAF7	441	Protein arginine methyltransferase NDUFAF7, mitochondrial; Arginine methyltransferase involved inside assembly or even stability of mitochondrial NADH:ubiquinone oxidoreductase complex (complex I). Acts by mediating symmetric dimethylation of 'Arg-118' of NDUFS2 after it assembles into complex I, stabilizing early intermediate complex; Belongs to NDUFAF7 family
9606.ENSP00000002165	FUCA2	467	Plasma alpha-L-fucosidase; Alpha-L-fucosidase catalyzes hydrolysis of alpha-1,6-linked fucose attached to glycoprotein carbohydrate moieties' reducing-end N-acetylglucosamine; it is classified within glycosyl hydrolase 29 family.

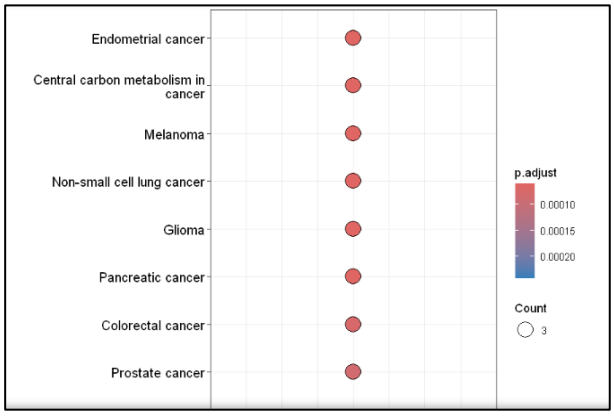

Figure 1: Study's cancer-related data with statistical significance (p. adjust).

Different cancers are shown on the y-axis, and the x-axis shows cancers' p values. The size of dots shows number of observations, and colors depict range of p values.

Almost all functions in biology rely on PPIs, thus their study is fundamentally important for understanding normal physiology as well as pathology. Interactions may be stable—for instance, those that constitute complexes such as the ribosome—or they may be fleeting, as seen in signaling pathways; in all cases, they occur between particular binding sites of proteins and serve defined biological functions. PPIs, in the form of protein-protein interaction networks (PPINs), can be studied mathematically and yield valuable information about cellular processes. The study of PPIs facilitates drug design, enables the inference of functions for previously unstudied proteins, allows for detailed examination of signaling pathways, and supports research into the construction of complex protein machines such as the proteasome. Figure 2, on the other hand, shows the growing complexity of the interactome made possible by advanced large-scale screening methods and mass spectrometry, hence highlighting the depth and breadth of known PPIs. These numbers taken together highlight the need of PPINs in disease modeling and scientific research.

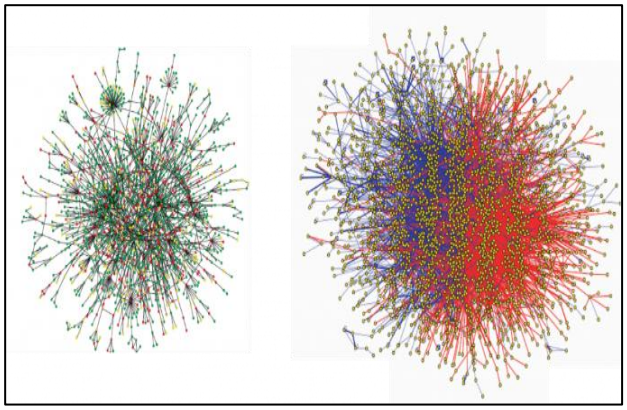

Figure 2: Illustrating the significance levels (adjusted p values) of various cancer types.

A subset of a PPI network emphasizes particular proteins and their direct connections inside a larger network. In diabetes research, such a subset might draw attention to important proteins as INS, GCK, IGF1, PPARG, and GLUT4 connected to insulin signaling and glucose control. As shown in Figure 3, this focused perspective enables researchers to grasp important molecular processes and interactions connected to diabetes.

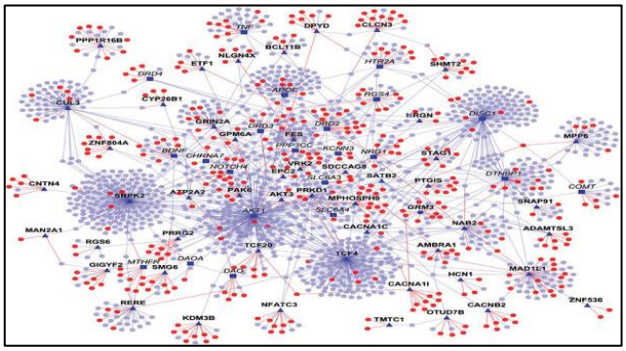

Figure 3: Subset of a PPI.

Figure 3 displays a section of a PPI network that zooms in on the proteins that have a function in diabetes. This segment contains key proteins like INS (insulin), GCK (glucokinase), IGF1 (insulin-like growth factor 1), PPARG (peroxisome proliferator-activated receptor gamma), and GLUT4 (glucose transporter type 4). Within the network, the nodes stand for proteins, and the edges stand for interactions, which illustrate the fundamental proteins and their interactions within and between biological pathways that are essential for diabetes, specifically glucose metabolism and insulin signaling. Proteins are represented as nodes in a PPI network, and the interactions between them are represented as edges. With PPI networks, diabetes research can effectively identify the key molecular interactions that relate to insulin signaling and glucose metabolism. Proteins like insulin (INS), glucokinase (GCK), IGF1, and PPARG play a vital role in glucose homeostasis and metabolic control. Delving deeper into a PPI network aids in understanding the complex mechanisms of diabetes as well as the mechanisms that can be targeted for treatment.

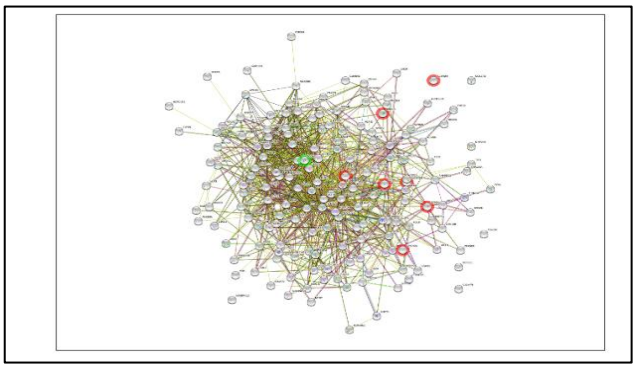

Figure 4: PPI network for diabetes.

The image illustrates a PPI network primarily focused on diabetes, showing protein interactions relevant to the disease. INS, GCK, IGF1, and PPARG, the pivotal proteins, are outlined in the network. The network's congested linking represents a significant number of interactions that need to be decoded for glucose metabolism, insulin signaling, and other biological functions relating to the diabetic disease.

DISCUSSION

Findings from the study add to the growing knowledge base that, despite presenting very differently in a clinical context, cancer and diabetes share overlapping molecular networks. Studies done earlier have revealed that persistent metabolic diseases like type 2 diabetes raise the likelihood of several malignancies, including pancreatic, liver, and endometrial cancers.[7] By finding proteins like PPARG, INS, and GCK, which not only control glucose and lipid metabolism but also engage in proliferative and inflammatory signaling pathways often changed in cancer, our PPI network analysis confirms this link.[8,9]

For example, FKBP4 found in our sample has been linked to tumor growth and neural control and is known to interact with steroid hormone receptors (Ebong et al). Likewise, retinoic acid's metabolism by CYP26B1 is important for cell differentiation and germ cell formation; its aberrant activity has been connected to cancer and infertility (Taimi et al). The discovery of NDUFAF7, a mitochondrial methyltransferase, further supports earlier research underlining mitochondrial dysfunction as a shared characteristic in cancer progression as well as metabolic disorders.[10] Using modified p-values to assess the strength of correlation across protein subsets and disease phenotypes, our work adds cancer-type particular relevance levels to the existing body of work. The reported statistical enrichment in pathways such central carbon metabolism, insulin signaling, and receptor-mediated transport in different cancers-e.g., glioma, melanoma, and non-small cell lung cancer-matches results from Saik and Kilmontov, who showed metabolic reprogramming as a hallmark of both cancer cells and insulin-resistant tissues.[11]

This integrated PPI study not only verifies earlier known connections across cancer and diabetes-related pathways but also emphasizes new proteins-such as ARF5 and FUCA2-whose interactions might have underexplored effects in disease progression. These results highlight the need of network-based methods in locating important molecular players and possible treatment targets spanning several complicated disorders.

CONCLUSION

This study demonstrates the utility of PPI subnetworks in revealing critical protein roles in disease-related biological systems. Proteins such as INS, GCK, and PPARG serve as central regulators in diabetes-associated networks, providing a molecular framework for understanding disease mechanisms. Additionally, the association of these networks with multiple cancer types highlights their broader biomedical significance. Such integrative analyses contribute to identifying candidate targets for diagnosis, treatment, and drug development in complex diseases.

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