Oncology
and Radiotherapy ©
17 (8) 2023: 249-253 • RESEARCH ARTICLE

Exploring the significance of zone 1 in human protein interaction networks: Identifying potential therapeutic targets for cancer treatment

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ABSTRACT

Protein-protein interaction networks are important tools for understanding the complex nature of biological processes and diseases, particularly cancer. However, the large size and complexity of these networks make it difficult to identify the most critical nodes that play important roles and act as critical regulators or mediators of biological processes in the networks. Identifying these key nodes within protein-protein interaction networks across different cancer types is crucial for elucidating the underlying molecular mechanisms and identifying potential therapeutic targets. Therefore, this study aims to analyse the significance of zone 1 in the human protein interaction network using the graph theory tool to identify the potential most important nodes across various cancer types.

Key words: protein-protein interaction networks; modelling; intersection cancer networks

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Word count: 2871 **Tables:** 05 **Figures:** 00 **References:** 24

Received:- 31 May, 2023, Manuscript No.: OAR-23-100386

Editor Assigned: 18 June, 2023, PreQC No.: OAR-23-100386 (Q)

Reviewed: 29 June, 2023, QC No.: OAR-23-100386 (PQ)

Revised: 24 July, 2023, Manuscript OAR-23-100386 (R)

Published: 03 August 2023, Invoice No. J-100386

INTRODUCTION

In recent years, graph theory analysis has emerged as a powerful tool for unravelling the structural properties and functional significance of protein-protein interaction networks (PPIs). By representing proteins as nodes and their interactions as edges, graph theory enables a comprehensive exploration of the network's topological features and facilitates the identification of key nodes that govern critical biological processes. This approach has been applied to various cancer types, including breast cancer, lung cancer and glioblastoma [1-3].

Several studies have successfully utilized graph theory analysis to identify key nodes in PPIs associated with specific cancer types. For instance, Fang E., et al., applied graph theory to analyse a breast cancer-specific protein-protein interaction network and identified key nodes that were significantly associated with disease progression and patient survival [4]. Their findings highlighted the importance of these nodes as potential prognostic markers and therapeutic targets in breast cancer. In another study, Jiang C., et al. utilized graph theory analysis to investigate PPIs in hepatocellular carcinoma [5]. By identifying key nodes based on centrality measures, they uncovered critical proteins involved in tumour progression, immune response, and drug resistance. Their findings provided valuable insights into the underlying molecular mechanisms and potential therapeutic avenues in hepatocellular carcinoma. Moreover, graph theory analysis has been employed to explore key nodes in PPIs across multiple cancer types [6]. Zhang and Wang conducted a comprehensive analysis of such networks using graph theory approaches and identified common key nodes that exhibited significant functional importance across various cancer types [7]. Their study emphasized the potential of these common key nodes as promising targets for broad-spectrum cancer therapies.

According to studies, graph theory analysis has been widely utilized to analyze PPIs in cancer research. In particular, the authors employed this method to identify hub proteins in breast cancer PPIs, as well as key nodes associated with lung cancer and their prognostic and therapeutic significance [8-10].

Recently study by Cohen AS, et al., employed graph theory analysis to characterize colorectal cancer PPIs [11]. Their findings revealed critical nodes that were implicated in tumour growth, invasion, and metastasis, underscoring the potential of graph theory analysis for identifying key players in cancer progression.

In this study, we aim to employ graph theory analysis for the

identification of crucial nodes in human protein interaction networks operating in multiple cancer varieties namely; Thyroid, Endometrial, Colorectal, Small cell lung, breast, Prostate, and Pancreatic [12]. We merge protein intersections that are prevalent in cancer-specific data and implement our previously established groundwork, which sorts proteins into zones as per their distance to the topological centre [13-15]. We comprehensively investigate zone 1, which is far one distance from the centre to discover important nodes linked with different cancer types. This study will contribute to our understanding of the molecular mechanisms underlying cancer and aid in the discovery of novel therapeutic targets tailored to specific cancer types.

METHODOLOGY

In this study, we use our novel approach, which treated PPIs as metric spaces and examined the distance between nodes using graph theory [13]. We utilized a python wrapper for the C++ Boost Graph Library (http://www.boost.org/) and implemented the Dijkstra algorithm. The purpose was to calculate the shortest distances between pairs of nodes. By identifying the nodes with the lowest maximum distance to other nodes, we were able to determine the network centre. Employing this methodology, we categorized nodes based on their distance from the centre and subsequently divided them into zones.

Analysis of pathways and functional enrichment

To determine the biological significance of different zones in the PPI network, proteins were grouped based on their distance from the center. An over-representation pathway analysis was performed on the protein groups associated with each zone. This analysis helped identify any specific functions that were attributed to those zones. To perform an enrichment analysis of the zones, various web services were used such as the gene set enricher in Comparative Toxigenomics Databases and enrichment analysis of Gene Ontology terms. A significance level of 0.01 was used as the threshold for statistical significance. Finally, to determine whether any zones exhibited functional specialization, the ratio of proteins participating in each enriched pathway was computed.

An evaluation of oncogene and tumor suppressor protein pathways

An assessment was carried out on protein scores, with special attention given to those found in oncogenes and tumour suppressors. Using information from genome-wide sequencing studies of cancer, enriched pathways were identified. In particular, the focus was on examining the interactions that obtained high scores. The results showed that these interactions commonly involved genes that were causally linked with cancer [16].

Proteins essential for cellular processes, signaling, growth, cell cycle regulation, and potential therapeutic targets

To evaluate the zone 1 of human functional protein interaction network, we identified a set of significant human proteins based on the knockout phenotypes of their corresponding genes in mice [17, 18].

RESULTS

In our previous study, we found that it is possible to model human PPIs as metric spaces [13]. These spaces were categorized proteins into different zones based on their distance from the centre, where hub proteins reside; these proteins are highly connected and essential in biological networks. Additionally, the study discovered that zones closest to the network centre contain vital proteins specialised for specific housekeeping functions. Furthermore, the study suggests that proteins located near the network centre could be potential therapeutic targets. In this study, we aim to extend our analysis to explore the significance of zone 1, which is the most highly connected zone and is of critical importance. Among other functions, zone 1 is enriched for proteins associated with signal transduction, immune system, haemostasis, and disease pathways, making it a core component for organismal and cellular sensing and response to environmental, biological, and mechanical stresses [14]. Zone 1 encompasses proteins engaged in various cellular functions, including cell cycle regulation; stress response, reproduction, and DNA damage response [19]. Our focus is on the 374 proteins that make up zone 1. To establish whether specific pathways are enriched in this zone, we mapped it to proteins in KEGG pathways [12]. Our investigation aims to identify the proteins involved in all KEGG "pathways in cancer," including the thyroid, endometrial, colorectal, small cell lung, breast, prostate, and pancreatic pathways (Table 1).

Distribution of Essential, signalling, growth, cell cycle, MAPK cascde, positive signalling and negative signalling in cancer-related proteins within zone 1

Cancer development and progression heavily rely on the activation and regulation of signalling pathways. Targeting signalling pathways in cancer is important because cancer cells often have altered and dysregulated signalling pathways that allow them to grow and survive, and targeting these pathways can affect their ability to do so [20-23].

In all types of cancer, the signalling proteins exhibit dominance over other functions with a proportion of 94.4%, followed by essential proteins with 79%. The remaining functions have the following proportions; cell cycle (40.8%), MAPK cascade

Tab. 1. Distribution of cancer-related proteins within zone 1

Type of cancer	Number of proteins
Thyroid	8
Endometrial	17
Colorectal	22
Small cell lung	30
Breast	36
Prostate	33
Pancreatic	35

(30.9%), negative signalling (29.8%), positive signalling (27%), and growth (18.2%) (Table 2).

Distribution of apoptosis, positive apoptosis, negative apoptosis, oncogenes tumour suppressor, and therapeutic target in cancer-related proteins within zone 1

Proteins are key players in cancer networks as they may be oncogenes (genes that promote cancer) or tumour suppressor genes (genes that prevent cancer), and their interactions influence the behaviour of cancer cells [24]. We found that oncogenes and successful therapeutic targets had the highest proportion at 15.4%. This finding provides clear evidence that this particular area contains a high concentration of proteins, indicating that some of them could potentially be good targets for drugs. Here are the proportions of the remaining functions tumour suppressor (12.7%), apoptosis (3.8%), negative apoptosis (2.7%) and positive apoptosis (1.1%) (Table 3).

Common proteins among types of cancer pathways and their function

Common proteins in cancer networks is very important because cancer is not caused by a single gene or protein, but rather by a network of interactions among various genes and proteins that regulate cell growth, division, and death. Due to this reason, we have identified two proteins, namely CCND1 and TP53 that are present in all cancer types that we are consider in our study. In addition, CCND1 and TP53 are essential, signalling, cell cycle and negative signalling proteins. Moreover, TP53 is growth protein and tumour suppressor.

Table 4 presents the distribution of protein intersectionality in various types of cancer, including endometrial, colorectal, small cell lung, breast, prostate, and pancreatic cancer. All of these proteins are signalling proteins and have not been targeted. Among them, PIK3CA and AKT1 are oncogenes while TP53 and PIK3R1 are tumour suppressors.

Finally, table 5 enlists the proteins that are commonly found in small cell lung, breast, prostate, and pancreatic cancer. It is observed that RB1 serves as an indispensable protein for various functions such as signalling, cellular growth, cell cycle regulation, negative signalling, and as a tumour suppressor.

DISCUSSION

The study analyses the significance of zone 1, the most highly connected zone in human protein interaction networks, and identifies proteins involved in various cancer pathways. Targeting dysregulated signalling pathways is important for cancer treatment, and the study found that in all types of cancer, the signalling proteins exhibit dominance over other functions with a proportion of 94.4%. Furthermore, we found that oncogenes and successful therapeutic targets had the highest proportion at 15.4%. This finding provides clear evidence that this particular area contains a high concentration of proteins, indicating that some of them could potentially be good targets for drugs. The study also identifies two essential proteins, CCND1 and TP53, are present in all cancer types considered. Finally, the study presents the

Tab. 2. Distribution of essential, signalling, growth, cell cycle, MAPK cascde, positive signalling and negative signalling in cancer-related proteins within zone 1

Cancer type	# of proteins	E	S	G	C	M	P/S	N/S
Thyroid	8	8 (100%)	8 (100%)	1 (12.5%)	4 (50%)	2 (25%)	2 (25%)	3 (37.5%)
Endometrial	17	13 (76.4%)	17 (100%)	2 (11.7%)	6 (35.2%)	8 (47%)	2 (11.7%)	6 (35.2%)
Colorectal	22	17 (77.2%)	22 (100%)	6 (27.2%)	8 (36.3%)	11 (50%)	6 (27.2%)	7 (31.8%)
Small cell lung	30	21 (70%)	27 (90%)	5 (16.6%)	15 (50%)	5 (16.6%)	10 (33.3%)	8 (26.6%)
Breast	36	28 (77.7%)	32 (88.8%)	4 (11.1%)	14 (38%)	11 (30%)	6 (16.6.5%)	11 (30.5%)
Prostate	33	27 (81.8%)	32 (96.9%)	8 (24.2%)	13 (39%)	9 (27.2%)	8 (24.2%)	10 (30.3%)
Pancreatic	35	29 (82.8%)	33 (94.2%)	7 (20%)	14 (40%)	10 (28%)	15 (42.8%)	9 (25.7%)

E=Essential, S=Signaling, G=Growth, C=Cell cycle, M=MAPK cascade, P/S=Positive signaling, N/S=Negative signaling

Tab. 3. Distribution of apoptosis, positive apoptosis, negative apoptosis, oncogenes tumor suppressor, and therapeutic target in cancer-related proteins within zone 1.

Cancer type	# of proteins	A	P/A	N/A	O	SG	T
Thyroid	8	1 (12.5%)	1 (12.5%)	0 (0%)	2 (25%)	1 (12.5%)	2 (25%)
Endometrial	17	0 (0%)	0 (0%)	0 (0%)	4 (23.5%)	2 (11.7%)	3 (17.6%)
Colorectal	22	1 (4.54%)	0 (0%)	1 (4.54%)	4 (18.1%)	2 (9.0%)	4 (18.1%)
Small cell lung	30	3 (10%)	1 (3.3%)	2 (6.6%)	3 (10%)	3 (10%)	4 (13.3%)
Breast	36	0 (0%)	0 (0%)	0 (0%)	4 (11.1%)	5 (13.8%)	5 (13.8%)
Prostate	33	1 (3%)	0 (0%)	1 (3%)	6 (18.1%)	5 (15.1%)	4 (12.1%)
Pancreatic	35	1 (2.8%)	0 (0%)	1 (2.8%)	5 (14.2%)	5(14.2%)	6 (17.1%)

A=Apoptosis, P/A=Positive apoptosis, A=Negative apoptosis, O=Oncogenes, S=Suppressor gene, T=Target protein

Tab. 4. Distribution of essential, signalling, growth, cell cycle, negative signaling, oncogenes and tumor suppressor in cancer-related proteins within zone 1

Cancer type (Endometrial, Colorectal, Small cell lung, Breast, Pancreatic) with their common protein	E	S	G	C	N/S	O	SG
CCND1	✓	✓	×	✓	✓	×	×
PIK3CA	✓	✓	×	×	×	✓	×
TP53	✓	✓	✓	✓	✓	×	✓
PIK3R1	×	✓	×	×	×	×	✓
AKT1	×	✓	✓	✓	×	✓	×

E= Essential, S= Signalling, G= Growth, C= Cell cycle, N/S= Negative signaling, O = Oncogenes, SG= Suppressor gene

Tab. 5. Distribution of essential, signaling, growth, cell cycle, negative signaling, oncogenes and tumor suppressor in cancer-related proteins within zone 1

Cancer type (Small cell lung, Breast, Prostate, Pancreatic) with their common protein	E	S	G	C	N/S	O	SG
E2F1	✓	×	×	✓	×	×	×
CCND1	✓	✓	×	✓	✓	×	×
PIK3CA	✓	✓	×	×	×	✓	×
TP53	✓	✓	✓	✓	✓	×	✓
PIK3R1	×	✓	×	×	×	×	✓
AKT1	×	✓	✓	✓	×	✓	×
RB1	✓	✓	✓	✓	✓	×	✓

E= Essential, S= Signaling, G= Growth, C= Cell cycle, N/S= Negative signaling, O = Oncogenes, SG= Suppressor gene

distribution of protein intersectionality in various cancers types, including small cell lung, breast, prostate, and pancreatic cancer, and identifies the protein RB1 as an indispensable protein for various functions and as a tumour suppressor. The study's findings provide valuable insights into the molecular mechanisms of cancer and highlight potential therapeutic targets.

CONCLUSION

Protein-protein interaction networks play a crucial role in understanding biological processes, especially cancer. However, due to the large size and complexity of these networks, identifying the most critical nodes in these networks can be challenging. Graph theory has proven effective in addressing this challenge by identifying key nodes within PPI networks. This study's goal was to use a novel accepted approach to highlight and determine the potential most important nodes in different cancer types' PPI networks (Tables 1 to 5) to elucidate the underlying molecular mechanisms and identify potential therapeutic targets. The results of this study could become a valuable resource for researchers and clinicians to identify and target crucial nodes in Zone 1 to develop effective treatments for cancer.

In conclusion, we recommend continued research in zones closer to centre in PPI networks to identify and target critical nodes in various diseases, particularly cancer. These endeavours will augment our understanding of the intricate molecular pathways involved in diseases, and accelerate the development of effective treatments.

FUNDING

This research was funded by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia (GRANT No.-3585).

AVAILABILITY OF DATA AND MATERIALS

Upon request from the corresponding author.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

The author would like to thank Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia for support.

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