

Original Research

Network Topology Similarities Across Cancer Types: Identifying Central Protein Hubs for Drug Discovery

Emad Fadhal^{1, 2, *}

1. Department of Mathematics & Statistics, College of Science, King Faisal University, P. O. Box 400, Al-Ahsa 31982, Saudi Arabia; E-Mail: efadhal@kfu.edu.sa
2. Department of Mathematics and Applied Mathematics, University of the Western Cape, Bellville, South Africa

* **Correspondence:** Emad Fadhal; E-Mail: efadhal@kfu.edu.sa

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Abstract

A molecular-level understanding of cancer is essential for the development of effective therapies. Constructing protein-protein interaction (PPI) networks offers a valuable approach to identifying dysregulated driver genes and potential therapeutic targets. In this study, we modeled cancer PPI networks as metric spaces and applied mathematical and computational algorithms to analyze their structural and functional properties. Our findings reveal that these networks share a conserved architecture across different cancer types, with central zones enriched in essential proteins and critical regulatory pathways. Notably, zones 1 and 2 of the cancer PPI networks are uniquely enriched in specific pathways, underscoring their importance in the progression of cancer. These results highlight the potential of metric-based analysis of PPI networks to uncover key molecular targets and accelerate drug discovery in oncology.

Keywords

Metric spaces; network modeling; cancer protein networks; core-periphery structure; drug discovery



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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, representing a significant public health concern. In recent years, advances in high-throughput technologies (including genomics, transcriptomics, and proteomics) have enabled researchers to uncover shared molecular features across different cancer types. Such integrative analyses have revealed that cancers, despite their tissue-specific distinctions, often share dysregulated pathways involving oncogenes, tumor suppressors, and cell signaling networks [1-5]. These insights have motivated efforts to identify common therapeutic targets, particularly by focusing on proteins and pathways that intersect across multiple cancer types [6].

Among the most promising tools for capturing these shared molecular landscapes are PPI networks, which offer a systems-level view of cellular organization and are essential for nearly all biological processes, including those underlying cancer initiation, progression, and metastasis [7-9]. Mapping cancer-related PPI networks allows for the identification of key driver genes and interaction hubs that are frequently altered across malignancies, offering valuable targets for therapeutic intervention [10-13]. Structural analysis of these networks has become a powerful strategy in drug discovery, as it uncovers conserved interaction patterns and topological similarities across cancer types [14-16].

Recent studies have approached cancer PPI networks as metric spaces, using mathematical models to analyze their modular structure and organizational principles [17-19]. Centrality measures, such as closeness and eccentricity, have revealed hierarchical zones within the network, distinguishing central hubs involved in information processing and cell cycle regulation from peripheral nodes associated with metabolic functions [20-22]. Notably, enrichment analyses have shown that proteins located in the central zones are more likely to be essential and functionally specialized, highlighting their potential as drug targets [23, 24].

Moreover, by integrating integrative cancer biology with network-based approaches, researchers have begun to construct integrated cancer PPI networks that highlight proteins shared among multiple cancer types. This framework not only identifies enriched biological pathways (such as oxidative phosphorylation, DNA repair, and immune regulation) but also reveals zones of functional convergence that could serve as universal therapeutic targets [25-27]. Several studies have demonstrated that different cancer types exhibit similarities in their PPI network topology, suggesting that a shared molecular infrastructure may support cancer pathogenesis across tissues [28-30].

Recent advances in graph learning and topological analysis of biological networks have introduced methods such as attributed graph embedding for protein-protein interaction link prediction [31], spectral clustering with graph structure learning [32], and affinity matrix construction integrating node attributes [33]. These methods excel in uncovering latent relationships and modular structures, but typically do not focus on stratifying networks into concentric layers around a topological center. Our metric-space zoning framework complements these approaches by explicitly identifying and functionally profiling core-periphery organization across 13 cancer types, enabling cross-cancer comparison of conserved functional hubs and facilitating integration with essential gene and drug-target datasets. This combination of topological

zoning and comparative enrichment analysis provides biologically interpretable insights that extend beyond conventional clustering or embedding methods.

In this study, we investigated the structural similarities and differences among PPI networks across 13 types of cancer. While each cancer type has distinct molecular and clinical features, many share disrupted biological processes, including cell signaling, metabolism, and DNA repair. By constructing cancer PPI networks that integrate proteins and pathways shared across cancers, we aimed to uncover central zones enriched with essential proteins and functional pathways that may serve as universal therapeutic targets.

2. Materials and Methods

2.1 Data Sources

We considered the HFPIN [34], which contains 9,448 nodes and 181,706 interactions. Gene expression presence/absence calls were obtained for multiple cancer types, including breast, lung, kidney, pancreatic, liver, cervical, ovarian, glioblastoma, pituitary gland, glioma, fallopian tube, endometrium, and rectum. These data were retrieved from the Gene Expression Barcode Database (<https://www.hsls.pitt.edu/obrc/index.php?page=URL20110523150503>). Genes expressed in at least 99% of samples of a specific cancer were selected against the human hgu133 background [35]. The “consistently expressed” designation required presence calls in $\geq 99\%$ of samples, ensuring robust inclusion across patients. Expression values were background-corrected to the hgu133 platform to maintain cross-cancer comparability.

2.2 Network Construction

We constructed cancer-specific protein interaction networks by mapping tumor-expressed proteins onto the human interactome (Figure 1). The algorithm followed these steps:

- (1) Build a graph G across the binary protein–protein interaction list of HFPIN;
- (2) Identify tumor proteins consistently expressed in cancers into a list L ;
- (3) Construct the interaction data between them from graph G if the proteins are in list L ;
- (4) Output the induced graph G' .

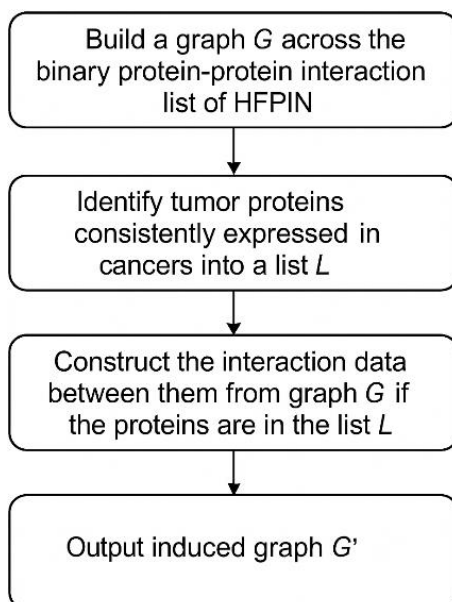


Figure 1 Generation of cancer-specific protein interaction graphs from the human interactome.

2.3 Metric Space and Zoning Framework

To evaluate interaction networks as metric spaces, we applied a graph-theoretic approach in which cancer PPI networks were modeled by defining the topological distance between proteins as the shortest path between nodes. This approach formalizes the concept of a metric space, where distance reflects the number of steps (edges) separating two proteins. Using a Python wrapper around the C++ BOOST graph library (<http://www.boost.org/>), we employed Dijkstra’s algorithm to compute shortest distances between all pairs of nodes. Based on these pairwise distances, the eccentricity of each node (defined as the maximum shortest path length from that node to any other node) was calculated. The node (or nodes) with the minimum eccentricity was designated as the network centre, representing the most centrally located point(s). Each remaining node was assigned to a “zone” based on its shortest distance from the centre. For instance, proteins located one step away formed zone 1, two steps away formed zone 2, and so forth (Figure 2). Zone assignments were validated by cross-referencing with alternative centrality measures to ensure consistency. This zoning framework enabled structural and functional analysis, revealing patterns such as central enrichment of essential or functionally specialized proteins.

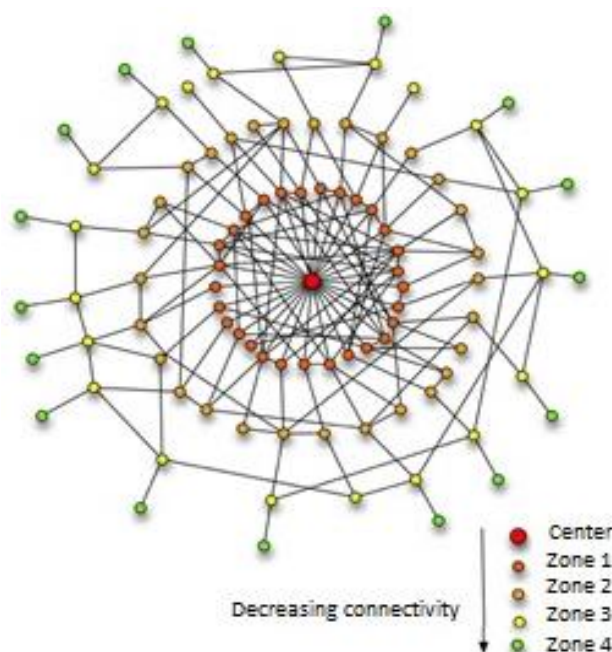


Figure 2 Cancer PPI networks organized into zones according to their distance from the network centre.

In contrast to earlier applications of zoning to single network types, here the method is extended to a multi-cancer setting, coupled with zone-specific enrichment analysis against curated biological databases. This ensures that the observed core enrichment patterns are both reproducible and biologically meaningful.

2.4 Functional Enrichment Analysis

To assess the robustness of our zoning framework, we performed two additional analyses: (i) enrichment significance testing using FDR correction ($q < 0.05$), and (ii) leave-one-cancer-type-out cross-validation to evaluate the stability of identified central hubs and enriched pathways. Across all tests, the zoning structure, core hubs, and zone 1-2 enrichment profiles remained stable, providing support for the reliability of our approach.

For enrichment analysis, we used the Comparative Toxicogenomics Database (CTD; <https://ctdbase.org/>). A p-value threshold of 0.01 was chosen to define significance. Results included enriched gene sets, statistical significance, and enrichment scores, providing insight into the biological processes and molecular functions associated with the input gene list.

2.5 Protein Class Annotation

We evaluated the distribution of oncogenes, tumor suppressors, and their associated pathways using genome-wide sequencing studies of cancer [36]. To identify key proteins within the cancer PPI networks, we intersected a list of previously defined essential proteins (derived from knockout phenotypes of mouse orthologs) with the proteins assigned to each zone [37]. This allowed us to assess the enrichment of essential proteins across zones and highlight the functional significance of core zones.

2.6 Robustness and Random Graph Controls

To test the biological significance of the observed topologies, we compared each cancer PPI network to a large set of computationally generated uniform random power-law graphs with similar node and edge counts [38]. While all cancer PPI networks exhibited a single centre and large diameter, the random equivalents often contained multiple centres and smaller diameters. Cancer PPI networks also had a higher proportion of low-degree “quill” nodes and a few extremely high-degree hubs, absent in random graphs. Moreover, the cancer networks consistently formed a single giant component, in contrast to the fragmented structures of many random equivalents. These differences indicate that the observed zoning patterns are not random artifacts but rather reflect a biologically evolved organization.

2.7 Visualization

Zone-level enrichment heatmaps were generated in Python (matplotlib), with pathways as columns and zones as rows. Cells display average (%) enrichment; missing cells indicate pathways not observed at FDR-controlled significance in that zone.

3. Results

3.1 Infrastructure of Individual Proteins in Cancer PPI Networks

We considered tumor proteins in HFPIN that are consistently expressed. Most cancers exhibited a high number of consistently expressed proteins (namely, rectum, endometrium, fallopian, glioma, pituitary, glioblastoma, ovary, cervix, liver, and pancreas), whereas breast, lung, and kidney cancers had the fewest. Across cancers, ~600 proteins were consistently expressed on average. In addition, tumor PPI networks contained fewer expressed proteins than their corresponding normal tissues (Table 1).

Table 1 Distribution of the normal and tumor proteins in HFPIN.

Type of cancer	# of proteins in normal	# of proteins in tumor
Breast	2088	258
Lung	2073	409
Kidney	1173	451
Pancreas	-	581
Liver	1313	583
Cervix	906	593
Ovary	1452	640
Glioblastoma	-	874
Pituitary	-	916
Glioma	-	972
Fallopian	1861	1089
Endometrium	1401	1291
Rectum	-	1379

3.2 Similarity between Cancer PPI Networks as Metric Spaces

We constructed 13 protein interaction networks representing pancreatic, kidney, lung, breast, cervical, glioblastoma, liver, ovarian, fallopian, glioma, rectal, endometrial, and pituitary cancers. Network properties and their structural similarities are summarized in Table 2 and Table 3. Several recurring features emerged:

- (i) Ten PPI-nets (breast, kidney, cervix, pancreas, ovary, glioblastoma, pituitary, glioma, liver, and lung) share RPS27A as the centre. RPS27A plays a significant role in targeting cellular proteins [39], underscoring its potential as a cancer drug target, particularly given its central role in protein synthesis. Two cancers (endometrium and fallopian) have XPO1 as the centre; XPO1 modulates the localization of cyclin B, MPAK, and MAPKAP kinase 2 [40]. Finally, rectum cancer has TP53 as its centre; TP53 is a core cell-cycle/apoptosis and DNA-damage control pathway component and a tumor suppressor in many tumor types [41].
- (ii) Proteins closer to the topological centre tend to have a higher degree.
- (iii) The majority of nodes reside within zones 1-3 relative to the centre.
- (iv) Nodes farther from the centre predominantly have low degree; at the periphery, most are single-degree (“quill”) proteins.
- (v) Most PPI-nets contain six zones around the centre; the fallopian, lung, and liver have five. Consistent with [18], modelling these networks with distance-respecting topology reveals a densely connected core that thins towards the periphery, ending in quills (degree = 1). Zone 1 is highly connected and contains very few low-degree proteins. The proportion of quills increases approximately exponentially with distance from the centre.

Table 2 Similarity between cancer PPI networks.

Type of cancer	Nodes	Edges	Components	The size of a giant	Diameter	Centre
Breast	258	2724	10	227	9	RPS27A
Kidney	451	4751	13	420	10	RPS27A
Cervix	593	6606	10	573	9	RPS27A
Pancreas	581	6434	15	547	10	RPS27A
Ovary	640	7138	12	615	9	RPS27A
Glioblastoma	874	8321	12	843	10	RPS27A
Pituitary	916	9087	24	859	9	RPS27A
Glioma	972	9348	18	930	10	RPS27A
Liver	583	6398	8	568	9	RPS27A
Lung	409	4473	8	389	9	RPS27A
Endometrium	1291	12610	33	1222	10	XPO1
Fallopian	1089	11286	22	1044	9	XPO1
Rectum	1379	14123	30	1314	10	TP53

(i) The networks consist of a single node. (ii) Some of them share the same centre.

Table 3 Distribution and similarity of zones around the cancer PPI networks.

Zones around the centre							
	1	2	3	4	5	6	
Breast	79	64	50	24	8	1	Nodes
	53	13	2	1	2	1	Avg degree
	67	31	13	4	5	1	High degree
Kidney	111	117	135	41	13	2	Nodes
	61	12	7	2	2	2	Avg degree
	83	37	28	6	5	3	High degree
Cervix	128	199	182	40	21	2	Nodes
	56	22	4	5	16	1	Avg degree
	86	76	30	26	22	1	High degree
Pancreas	124	198	162	54	6	2	Nodes
	58	19	4	15	2	2	Avg degree
	85	66	33	32	5	2	High degree
Ovary	127	181	240	56	9	1	Nodes
	59	23	8	1	1	1	Avg degree
	87	76	35	4	2	1	High degree
Glioblastoma	132	251	363	79	14	3	Nodes
	59	23	7	2	1	1	Avg degree
	91	80	34	6	4	1	High degree
Pituitary	135	272	362	77	11	1	Nodes
	58	24	9	1	1	1	Avg degree
	98	84	43	6	2	1	High degree
Glioma	138	280	396	89	21	5	Nodes
	58	23	8	1	1	2	Avg degree
	96	87	43	7	7	3	High degree
Liver	123	154	210	71	9	0	Nodes
	58	21	3	2	1	0	Avg degree
	84	65	35	10	17	0	High degree
Lung	105	123	111	28	21	0	Nodes
	61	12	4	4	10	0	Avg degree
	84	41	15	20	17	0	High degree
Endometrium	89	530	493	95	11	3	Nodes
	38	33	7	2	1	1	Avg degree
	67	31	13	4	5	1	High degree
Fallopian	85	457	419	73	9	0	Nodes
	53	13	3	1	2	0	Avg degree
	107	149	41	6	1	0	High degree
Rectum	97	661	398	133	23	1	Nodes
	23	32	5	13	1	1	Avg degree
	160	117	45	42	3	1	High degree

(i) The nodes in the central position have a high degree. (ii) The majority of the nodes are 3

distances away from the centre.

Robustness analyses confirmed the stability of these findings, as leave-one-cancer-type-out analysis preserved >85% of enriched pathways in zones 1-3 across cancers. All reported pathway enrichments are FDR-adjusted ($q < 0.05$) (Table S1).

3.3 Similarity Based on Dominant Biological Functions

Enrichment analyses revealed similar dominant biological functions across cancers. The average percentages were 31%, 24.9%, 19.7%, 18.6%, 18.3%, 13.1%, 12.6%, 9.9%, 7.7%, and 6% for gene expression, disease, metabolism of RNA, metabolism of proteins, immune system, signal transduction, 3'-UTR-mediated translational regulation, cell cycle, mitotic M-M/G1 phases, and apoptosis, respectively (Tables S2-S14). Further, their Representation of immune system pathways appeared approximately equal across cancers, consistent with the immune hallmarks of cancer [26, 42]. Moreover, immune surveillance and recognition/clearance of nascent tumors have long been described as central immune functions [27, 28].

We next examine cancer-specific PPI-nets to identify pathways that are uniquely enriched across zones of each cancer type. In general, central zones are implicated in sensing/regulatory functions that control cancer, whereas peripheral zones diversify into routine metabolic functions.

3.4 Zone-Level Biological Observations Across Cancers

3.4.1 Cancers with RPS27A as Centre

We refer to cancers centred on RPS27A as “RPS27A cancers”. In 10 such cancers (breast, kidney, cervix, pancreas, ovary, glioblastoma, pituitary, glioma, liver, and lung), zone 1 exhibits the highest percentage of proteins involved in critical functional pathways, followed by zone 2; peripheral zones are enriched for metabolic pathways (Tables S15-S27). Three pathways are uniquely enriched in RPS27A cancers: in zone 1, 3'-UTR-mediated translational regulation and ribosome; in zone 2, mRNA processing. Figure 3, Figure 4, Figure 5 present zone-specific enrichment heatmaps.

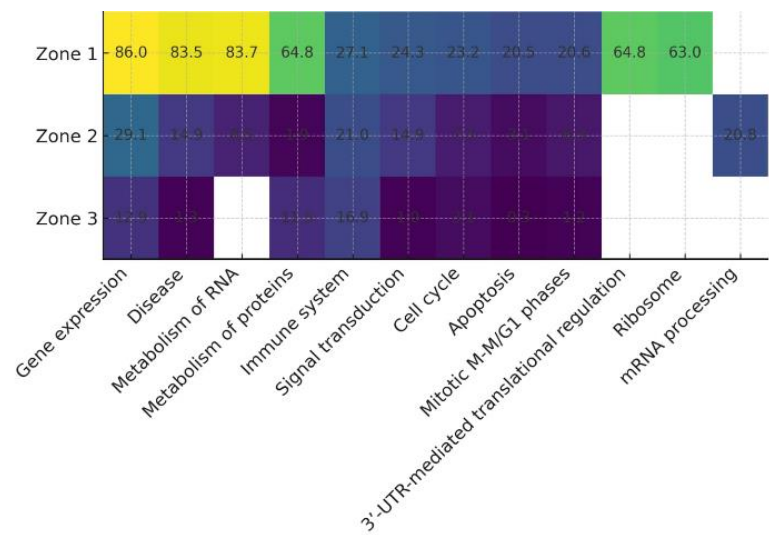


Figure 3 RPS27A-centred cancers: Zone-specific enrichment across major functional pathways.

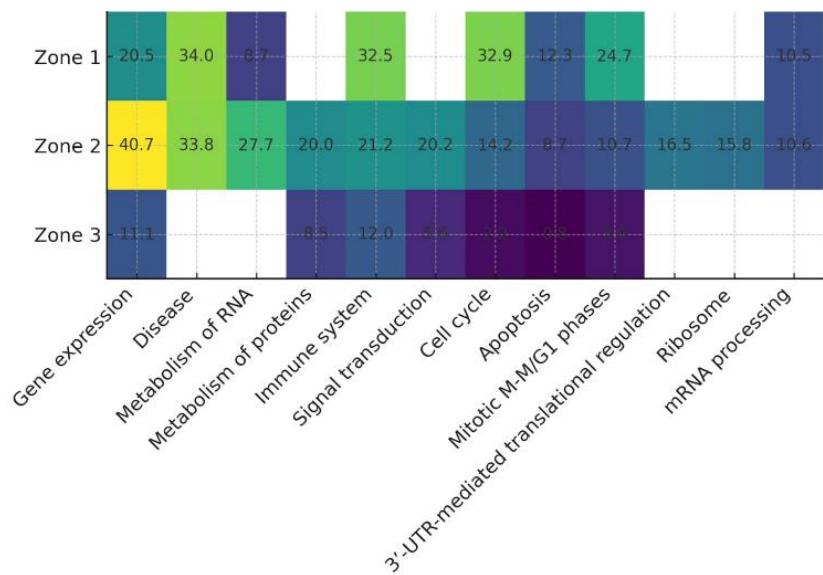


Figure 4 XPO1-centred cancers: Zone-specific enrichment.

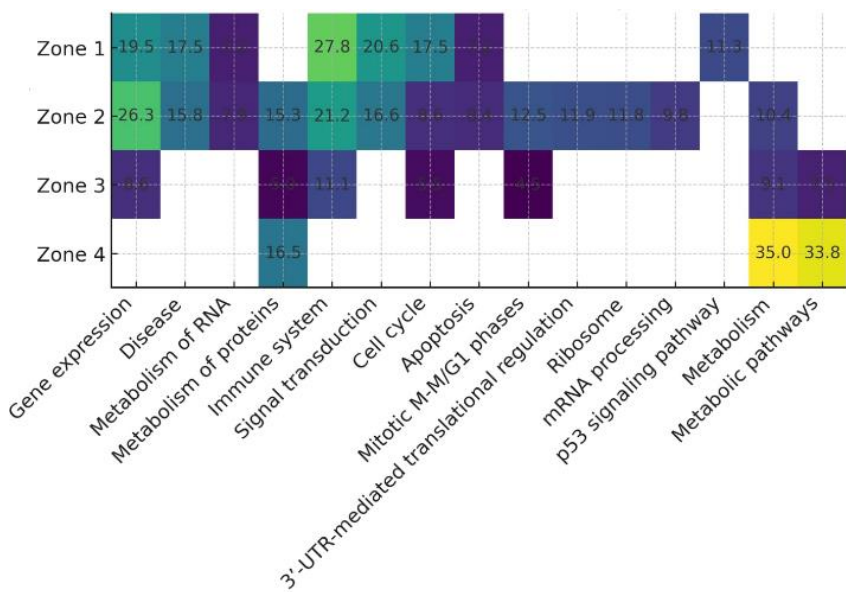


Figure 5 TP53-centred cancers: zone-specific enrichment.

Zone 1. The summary of functional pathways in zone 1 of Table 4 summarizes zone 1 pathways for RPS27A cancers. The average percentages were 86%, 83.7%, 83.5%, 64.8%, 64.8%, and 63% for gene expression, RNA metabolism, 3'-UTR-mediated translational regulation, and ribosome function, respectively. The latter two are uniquely enriched in zone 1. 3'-UTR-mediated translational regulation is implicated in tumorigenesis and metastasis [29], and ribosome biogenesis has been linked to malignant progression and is inhibited by several anti-cancer drugs [30, 41]. These observations underscore the biological importance of zone 1 proteins and their potential as novel drug targets.

Table 4 Summary of functional pathways in zone 1 of RPS27A cancers.

Enriched Pathway	Breast	Kidney	Cervix	Pancreas	Ovary	Glioblastoma	Pituitary	Glioma	Liver	Lung	Average
Gene expression	91.1%	91.9%	83.5%	84.6%	86.6%	84%	82.9%	82.6%	86.1%	87.6%	86%
Disease	89.8%	90.9%	68.9%	68.2%	86.6%	84.8%	85.9%	85.5%	86.9%	87.6%	83.5%
Metabolism of RNA	89.8%	90%	81.2%	81.4%	84.2%	81%	80.7%	80.4%	83.7%	84.7%	83.7%
Metabolism of proteins	79.7%	69.3%	58.5%	62%	61.4%	59%	57%	56.5%	62.6%	73.3%	64.8%
3'-UTR-mediated translational regulation	79.7%	69.3%	58.5%	62%	61.4%	59%	57%	56.5%	62.6%	73.3%	64.8%
Ribosome	78.4%	68.4%	57.8%	61%	60.6%	58%	56.2%	55.7%	61.7%	72.3%	63%
Immune system	15.1%	26.1%	30.4%	28.2%	30.7%	31%	30.3%	32.6%	29.2%	18%	27.1%
Signal transduction	-	26.1%	28.9%	26.6%	27.5%	28.7%	30.3%	31.1%	26%	18%	24.3%
Cell cycle	13.9%	22.5%	27.3%	24.1%	25.9%	26.5%	26.6%	27.5%	23.5%	14.2%	23.2%
Apoptosis	11.3%	20.7%	23.4%	20.1%	23.6%	22.7%	24.4%	24.6%	21.9%	12.3%	20.5%
Mitotic M-M/G1 phases	10.1%	20.7%	25%	21.7%	23.6%	23.4	24.4%	24.6%	21.1%	11.4%	20.6%
* mRNA processing	-	-	-	-	-	-	-	-	-	-	-
Number of proteins	79	111	128	124	127	132	135	138	123	105	-

* This function is uniquely enriched in other zones.

Breast cancer differs from other RPS27A cancers in lacking signal transduction enrichment in zone 1. Nevertheless, given the strong enrichment of this pathway in the different cancers, zone 1 proteins from this functional class may still represent attractive targets.

Zone 2. Table 5 summarizes zone-2 pathways for RPS27A cancers. Gene expression (29.1%), the immune system (21%), and mRNA processing (20.8%) are the primary areas of focus. As noted earlier, mRNA processing is uniquely enriched in zone 2 of these cancers and is clinically relevant as both a driver of disease states and a potential biomarker. Additionally, mRNA processing targets and ribosomes are absent in zone 2 [42-44]. Signal transduction and cell cycle do not appear in breast cancer in this zone, and mitotic M-M/G1 phases are absent in breast, kidney, liver, and lung. Overall, zone 2 shows a less uniform functional similarity than zone 1.

Table 5 Summary of functional pathways in zone 2 of RPS27A cancers.

Enriched Pathway	Breast	Kidney	Cervix	Pancreas	Ovary	Glioblastoma	Pituitary	Glioma	Liver	Lung	Average
Gene expression	38%	24.1%	28.8%	29.5%	31.2%	25.1%	26.2%	26.3%	33.7%	28.6%	29.1%
Disease	14.2%	16.3%	17.2%	14.7%	16.2%	5.3%	19.1%	15.8%	17.2%	13.1%	14.9%
Metabolism of RNA	12.6%	8.6%	7.7%	7.1%	8.3%	7.2%	6.7%	7.9%	9.9%	9%	8.5%
Metabolism of proteins	-	-	-	-	7.6%	-	5.6%	-	7.2%	-	1.9%
* 3'-UTR-mediated translational regulation	-	-	-	-	-	-	-	-	-	-	-
* Ribosome	-	-	-	-	-	-	-	-	-	-	-
Immune system	15.8%	27.5%	23.7%	17.4%	20.1%	21.4%	20.9%	21.2%	22.5%	20.4%	21%
Signal transduction	-	18.9%	17.5%	15.8%	15%	18.6%	17.6%	16.6%	13.2%	16.3%	14.9%
Cell cycle	-	-	11.3%	9.1%	8.9%	9.3%	8.9%	8.6%	7.9%	7.3%	7.3%
Apoptosis	-	5.1%	4.1%	4%	-	3.1%	3.3%	3.2%	3.9%	4.9%	3.1%
Mitotic M-M/G1 phases	-	-	8.2%	5.1%	5%	6.8%	5.2%	6.1%	-	-	6.3%
mRNA processing	28.5%	19.6%	20.1%	20.9%	23.4%	17.4%	18.3%	17.3%	23.8%	19.6%	20.8%
Number of proteins	64	117	199	198	181	251	272	280	154	123	-

* Those functions are uniquely enriched in the other zone.

Zone 3. Table 6 lists zone-3 pathways for RPS27A cancers. As expected, average percentages of significant pathways are lower than in zones 1-2. Functions dominant in zones 1-2 largely disappear, except the immune system (16.9%), gene expression (12.9%), and metabolism of proteins (11.5%). This pattern is consistent with the hypothesis that functional dominance decreases with distance from the centre.

Table 6 Summary of functional pathways in zone 3 of RPS27A cancers.

Enriched Pathway	Breast	Kidney	Cervix	Pancreas	Ovary	Glioblastoma	Pituitary	Glioma	Liver	Lung	Average
Gene expression	16%	11.1%	10.4%	17.3%	13.8%	11.3%	12.5%	11.4%	14.7%	10.8%	12.9%
Disease	-	-	-	-	-	-	7.5%	6.1%	-	-	1.3%
Metabolism of RNA	-	-	-	-	-	-	-	-	-	-	-
Metabolism of proteins	18%	-	10.4%	17.6%	12.5%	8.6%	9.4%	8.4%	14.2%	14.4%	11.5%
* 3'-UTR-mediated translational regulation	-	-	-	-	-	-	-	-	-	-	-
* Ribosome	-	-	-	-	-	-	-	-	-	-	-
Immune system	32%	15.5%	13.1%	16.7%	13.3%	14.4%	10%	13.5%	18.5%	22.5%	16.9%
Signal transduction	-	-	-	-	-	10.8%	-	-	-	-	1%
Cell cycle	-	-	7.1%	8%	-	5.2%	6.4%	4.5%	-	-	3.1%
Apoptosis	-	5.1%	-	-	-	-	3.3%	-	-	-	0.3%
Mitotic M-M/G1 phases	-	-	-	4.9%	-	3.6%	4.3%	-	-	-	1.2%
* mRNA processing	-	19.6%	-	-	-	-	-	-	-	-	-
Number of proteins	50	135	182	162	240	363	362	396	210	111	-

* Those functions are uniquely enriched in the other zone.

3.4.2 Cancers with XPO1 as Centre

Cancers centred on XPO1 are referred to as “XPO1 cancers.” Overall enrichment dominance is lower than in RPS27A cancers. Pathways uniquely enriched in zone 1 of RPS27A cancers become uniquely enriched in zone 2 of XPO1 cancers; mRNA processing appears in both zones but not in zone 3.

Zone 1. Table 7 summarizes zone 1 pathways in XPO1 cancers. The most prominent pathways are disease (34%), cell cycle (32.9%), immune system (32.5%), mitotic M-M/G1 (24.7%), and gene expression (20.5%). Notably, signal transduction, protein metabolism, 3'-UTR-mediated translational regulation, and ribosomes are not represented here, despite being dominant in zone 1 of RPS27A cancers. Mitotic anti-cancer strategies have been revisited recently [45].

Table 7 Summary of functional pathways in zone 1 of XPO1 cancers.

Enriched Pathway	Endometrium	Fallopian	Average
Gene expression	20.6%	20.4%	20.5%
Disease	34.3%	33.7%	34%
Metabolism of RNA	9.1%	8.4%	8.7%
*Metabolism of proteins	-	-	-
* 3'-UTR-mediated translational regulation	-	-	-
* Ribosome	-	-	-
Immune system	32.5%	32.5%	32.5%
* Signal transduction	-	-	-
Cell cycle	31%	34.9%	32.9%
Apoptosis	12.6%	12%	12.3%
Mitotic M-M/G1 phases	22.9%	26.5%	24.7%
mRNA processing	10.3%	10.8%	10.5%
Number of proteins	89	85	-

* Those functions are uniquely enriched in the other zone.

Zone 2. Table 8 summarizes zone-2 pathways in XPO1 cancers. Gene expression increases to 40.7% (approximately double that of zone 1). Pathways uniquely enriched in zone 1 of RPS27A cancers (e.g., 3'-UTR-mediated translational regulation, ribosome) become uniquely enriched in zone 2 here. Signal transduction also appears in zone 2. These observations reinforce the potential of zone-2 proteins in XPO1 cancers as novel targets.

Table 8 Summary of functional pathways in zone 2 of XPO1 cancers.

Enriched Pathway	Endometrium	Fallopian	Average
Gene expression	38.4%	43.1%	40.7%
Disease	32.6%	35.1%	33.8%
Metabolism of RNA	26.6%	28.9%	27.7%
Metabolism of proteins	19.3%	20.7%	20%
3'-UTR-mediated translational regulation	14.9%	17.2%	16.5%

Ribosome	14.7%	17%	15.8%
Immune system	21.2%	21.2%	21.2%
Signal transduction	19.8%	20.7%	20.2%
Cell cycle	13.9%	14.6%	14.2%
Apoptosis	8.4%	9%	8.7%
Mitotic M-M/G1 phases	10.5%	11%	10.7%
mRNA processing	10.1%	11.2%	10.6%
Number of proteins	530	457	-

Zone 3. Again, in zone 3, several functions are absent (disease, 3'-UTR-mediated translational regulation, ribosome, and mRNA processing). Signal transduction appears in the endometrium but not the fallopian tubes. Overall averages in zone 3 are weaker than those in zones 1-2 (Table 9).

Table 9 Summary of functional pathways in zone 3 of XPO1 cancers.

Enriched Pathway	Endometrium	Fallopian	Average
Gene expression	10.9%	12%	11.1%
* Disease	-	-	-
* Metabolism of RNA	-	-	-
Metabolism of proteins	8.5%	8.6%	8.5%
* 3'-UTR-mediated translational regulation	-	-	-
* Ribosome	-	-	-
Immune system	12%	12%	12%
Signal transduction	11.2%	-	5.6%
Cell cycle	4.4%	-	2.2%
Apoptosis	1.6%	-	0.8%
Mitotic M-M/G1 phases	3%	3.1%	3%
* mRNA processing	-	-	-
Number of proteins	530	457	-

* Those functions are uniquely enriched in the other zone.

3.4.3 Cancers with TP53 as Centre

Table 10 presents functional pathways by zone for TP53-centred cancers. Zone 1 shows unique enrichment of the p53 signaling pathway; p53 is engaged in stress responses and supports targeted therapy development [46, 47]. In zone 2, 3'-UTR-mediated translational regulation, ribosome, and mRNA processing are uniquely enriched (again highlighting the central role of zones 1-2 in cancer biology and drug targeting).

Table 10 Functional pathways in TP53 cancer zones.

Enriched Pathway	Zone1	Zone2	Zone3	Zone4
Immune system	27.8%	21.2%	11.1%	-
Signal transduction	20.6%	16.6%	-	-
Gene expression	19.5%	26.3%	8.6%	-
Disease	17.5%	15.8%	-	-

Cell cycle	17.5%	8.6%	5.5%	-
p53 signaling pathway	11.3	-	-	-
Metabolism of RNA	7.2%	7.9%	-	-
Apoptosis	7.2%	8.4%	-	-
3'-UTR-mediated translational regulation	-	11.9%	-	-
Metabolism of proteins	-	15.3%	5%	16.5%
Ribosome	-	11.8%	-	-
Mitotic M-M/G1 phases	-	12.5%	4.5%	-
mRNA processing	-	9.8%	-	-
Metabolism	-	10.4%	9.1%	35%
Metabolic pathways	-	-	7.5%	33.8%
Number of proteins	97	661	398	133

3.5 Distribution of Essential, Signaling, Growth, Cell Cycle, Tumor Suppressor, Oncogenic, and Therapeutic-Target Classes

Class-distribution patterns were broadly similar across cancers (Table 11). Despite zone-specific differences in protein counts, percentage distributions across zones were comparable.

Table 11 Distribution of essential, signaling, growth, cell cycle, tumor suppressor, oncogenic, and therapeutic targets in cancer PPI-nets based on distance from the topological centre.

Type of cancer	# of proteins	Essential roles	Signaling	Growth	Cell cycle	Drug targets	Oncogenes	Tumour suppressors
Breast	227	47 (20.7%)	76 (33.3%)	3 (1.3%)	24 (10.5%)	9 (3.9%)	1 (0.4%)	2 (0.8%)
Pituitary	859	183 (21.3%)	306 (35.6%)	19 (2.2%)	95 (11%)	33 (3.8%)	9 (1%)	4 (0.4%)
Lung	389	85 (21.0%)	131 (33.6%)	7 (1.7%)	36 (9.2%)	18 (4.6%)	3 (0.7%)	2 (0.5%)
Kidney	420	88 (20.9%)	145 (34.5%)	9 (2.1%)	42 (10%)	23 (5.4%)	6 (1.4%)	2 (0.4%)
Liver	568	125 (22%)	194 (34.1%)	8 (1.4%)	56 (9.8%)	26 (4.5%)	9 (1.5%)	3 (0.5%)
Pancreas	547	123 (22.4%)	188 (34.3)	10 (1.8%)	71 (12.9%)	20 (3.6%)	8 (1.4%)	2 (0.3%)
Cervix	573	138 (24%)	187 (32.6%)	10 (1.7%)	80 (13.9%)	24 (4.1%)	10 (1.7%)	4 (0.6%)
Ovary	615	134 (21.7%)	197 (32%)	12 (1.9)	71 (11.5%)	24 (3.9%)	7 (1.1%)	5 (0.8%)
Glioblastoma	843	198 (23.4%)	325 (38.5%)	23 (2.7%)	95 (11.2%)	36 (4.2%)	11 (1.3%)	8 (0.9%)
Glioma	930	207 (22.2%)	334 (35.9%)	22 (2.3%)	98 (10.5%)	35 (3.7%)	10 (1%)	8 (0.8%)
Fallopian	1044	248 (23.7%)	356 (34%)	29 (2.7%)	132 (12.6%)	39 (3.7%)	11 (1%)	10 (0.9%)
Endometrium	1222	291 (23.8%)	463 (37.8%)	28 (3.1%)	141 (11.5%)	46 (3.7%)	12 (0.9%)	15 (1.2%)
Rectum	1314	286 (21.7%)	480 (36.5%)	30 (2.2%)	166 (12.6%)	56 (4.2%)	14 (1%)	12 (0.9%)
Average	-	22.2%	34.8%	2%	11.3%	4.1%	1.1%	0.6%

Signaling roles were the most prominent (34.8%), followed by essential (22.2%) and cell cycle (11.3%) functions. Below, we detail how each class is distributed across zones for each cancer type.

3.6 Protein-Class Distributions Across Zones

Using a conserved human essential gene list (Mouse Genome Database) [37], we observed the highest percentages of crucial proteins in central zones: zones 1-5 comprised 10.9%, 40%, 33%, 9.2%, and 1.1%, respectively (Table S28).

A similar pattern held for signaling proteins: 10%, 43%, 31.1%, 8.4%, and 1.0% in zones 1-5, respectively (Table S29).

Growth proteins (though fewer) were also central, with percentages of 12.7%, 34.5%, 43.5%, 8.9%, and 0.3% across zones 1-5 (Table S30), supporting the view that central zones are promising for drug targeting.

For the cell cycle, zones 1-2 dominated at 40.8% and 40.6%, followed by 15.5%, 1.7%, and 0%, respectively (Table S31). Dysregulated cell-cycle control underlies uncontrolled growth and genomic damage (hallmarks of cancer [48]).

Drug targets concentrated in zones 1-3: 8.7%, 45.7%, 39%, 5%, 0% (Table S32), further underscoring the translational value of central zones.

Oncogenes peaked in zone 2 (Table S33): 1.8%, 85%, 10%, 1.9%, and 0.9% across zones 1-5. Prior work links oncogenes/tumor suppressors to metastatic progression and essential tumor functions [47, 49, 50], supporting the focus on zone 2 as a reservoir of therapeutically relevant proteins.

Finally, tumor suppressors were enriched in zones 1-3, with high representation 1-2: 30.3%, 37.6%, 25.3%, 5.6%, and 0.9% across zones 1-5 (Table S34). Together with the oncogene pattern, this supports prioritizing central zones for target discovery.

4. Discussion

We introduced a network-biological approach that models cancer PPI networks as metric spaces. This framework reveals a conserved core-periphery organization across cancers, with central proteins (e.g., RPS27A, XPO1, and TP53) occupying the most connected zones and participating in key cellular programs. For instance, RPS27A is implicated in ribosome biogenesis and protein degradation [51], XPO1 regulates nuclear export and contributes to drug resistance [52], and TP53 is a critical tumor suppressor governing cell-cycle checkpoints and apoptosis [53].

Our work complements graph-learning methods by providing a mathematically transparent, interpretable scheme for zone identification. The observed centrality of RPS27A, XPO1, and TP53 is consistent with graph-embedding findings [54]. We extend these observations by demonstrating zone-specific functional enrichment across various types of cancer. Thus, integrating metric-based zoning with functional annotation offers a roadmap to prioritize targets supported by both topology and biology.

Regarding zone-level enrichment, cancers centred on RPS27A show clear dominance of core pathways in central zones. Zone 1 is the most dominant, uniquely enriched for 3'-UTR-mediated translational regulation and ribosome biogenesis, both of which are implicated in oncogenesis and are therapeutically actionable [55, 56]. Zone 2 remains functionally important and is uniquely enriched for mRNA processing, whereas zone 3 is comparatively attenuated. These patterns

highlight the critical role of near-centre proteins as potential drug targets, while more peripheral zones tend to be enriched for metabolic functions. Notably, signal-transduction pathways were not detected in zone 1 of RPS27A cancers (Figure 6).

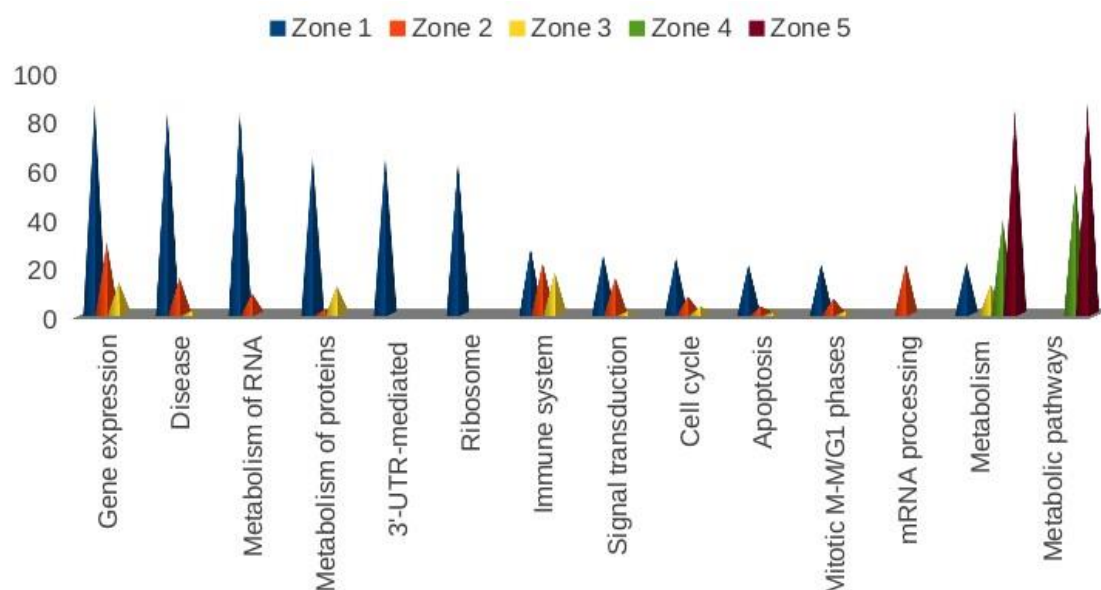


Figure 6 Dominant zones in GO enrichment functions in RPS27A cancers.

In XPO1-centred cancers, overall enrichment is slightly less pronounced than in RPS27A cancers, yet key shifts are evident. Pathways uniquely enriched in zone 1 of RPS27A cancers are also present in zone 2 of XPO1 cancers. Conversely, zone 1 of XPO1 cancers is enriched in cell-cycle, immune, and mitotic M-M/G1 processes, reinforcing the centrality of zone 1 proteins to cancer biology and the discovery of potential targets. Zone 2 exhibits dominance in RNA metabolism, gene expression, and protein metabolism, whereas zone 3 mirrors RPS27A cancers with predominantly metabolic activity (Figure 7).

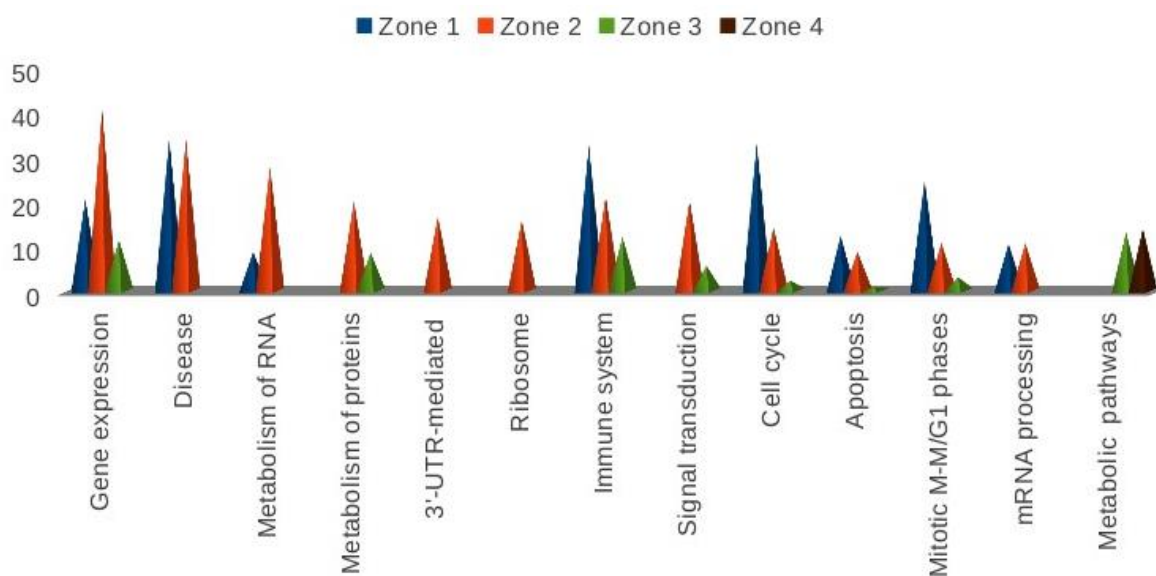


Figure 7 Dominant zones in GO enrichment functions in XPO1 cancers.

For TP53-centred cancers (notably rectum), overall enrichment is lower than in RPS27A and XPO1 cancers; however, zone 2 shows unique enrichment for 3'-UTR-mediated translational regulation, ribosome biogenesis, and mRNA processing, further underscoring the functional relevance of central zones (Figure 8) and aligning with their roles in cancer progression and regulation [57, 58].

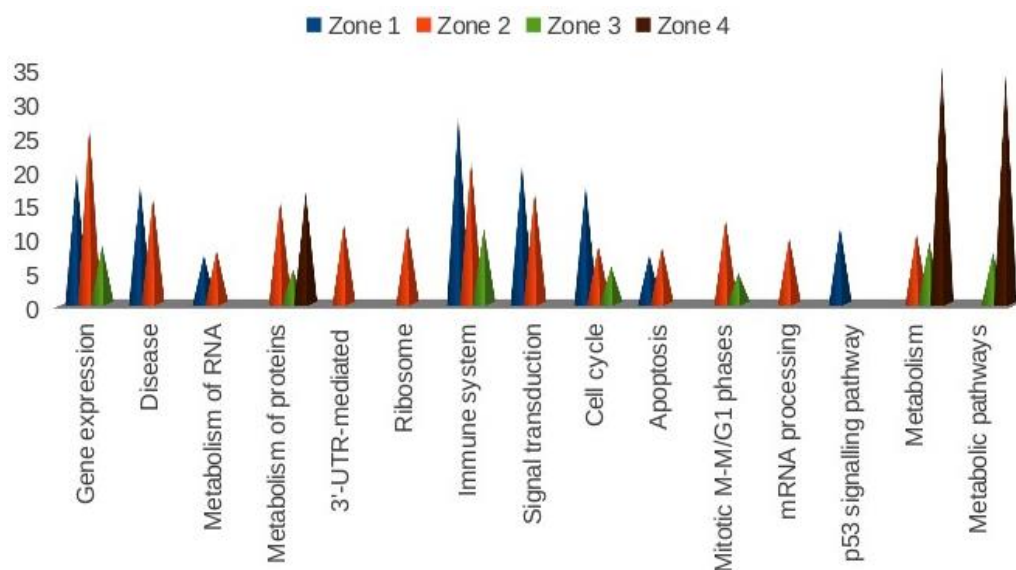


Figure 8 Dominant zones in GO enrichment functions in TP53 cancers.

A significant finding is the tendency of essential genes, oncogenes, and tumor suppressors to cluster in core zones (zones 1-3). For instance, 22.2% of essential genes and 34.8% of signaling proteins are central, consistent with theories of network centrality and tumor survival [59, 60]. Moreover, evidence from the cancer dependency map indicates that centrally located proteins are more likely to be critical dependencies [61].

Several central proteins highlighted here already have experimental or clinical validation. Inhibiting ribosomal RNA synthesis (e.g., CX-5461) demonstrates antitumor activity, aligning with the role of RPS27A in ribosome biogenesis/protein turnover [62, 63]. XPO1 is clinically targetable with selinexor, which disrupts nuclear export and impairs tumor proliferation [64]. TP53 remains the prototypical tumor suppressor with ongoing efforts to restore function clinically. In addition, enrichment of 3'-UTR regulation, ribosome biogenesis, and mRNA processing is supported by experimental studies linking the disruption of these processes to oncogenesis [65]. Collectively, these observations externally validate our computational predictions and strengthen their translational relevance, while also motivating laboratory experiments to confirm novel predictions.

Although based on computational analyses, our results emphasize the need for experimental validation. Future studies should test whether targeting central-zone proteins improves therapeutic outcomes and examine how peripheral, metabolically enriched proteins may contribute to drug resistance.

In summary, modeling cancer PPI networks as metric spaces provides a powerful lens for uncovering shared network architectures and functional liabilities across cancers. The repeated dominance of ribosome, mRNA processing, and 3'-UTR-mediated regulation in zones 1-2 indicates that these zones house key, biologically central proteins with therapeutic promise [66, 67]. A data-level limitation is the absence of patient and subtype-specific variation in the expression inputs.

While our consensus-network strategy facilitates cross-cancer comparability, it may overlook clinically meaningful heterogeneity. Future work should incorporate individual-level datasets to delineate pan-cancer targets alongside subtype-restricted vulnerabilities.

A methodological limitation is that eccentricity-based zoning assumes an essentially connected network with a single dominant centre (or a small co-central set). This assumption held across the 13 cancers analysed, but networks with unusually high modularity, multiple dense hubs, or fragmented components may deviate. In such cases, zones should be computed per significant component or module to preserve biological interpretability. Extending the zoning framework to multi-centre or fragmented architectures is an essential direction for methodological development.

5. Conclusions

The construction of cancer PPI networks provides a valuable framework for drug discovery by offering a systems-level view of the molecular interactions underlying cancer progression. Identifying dysregulated driver proteins and pathways within these networks can guide the development of therapeutic strategies. In this study, we modeled cancer PPI networks as metric spaces and applied mathematical and computational algorithms to uncover critical structural and functional properties.

Our findings demonstrate that cancer PPI networks share a conserved metric-space organization, with central zones enriched for essential proteins and key functional pathways. These proteins control fundamental cellular decisions, including pathway regulation, and are disproportionately concentrated in the core regions of the cell. Notably, zones 1 and 2 exhibited unique enrichment in pathways central to cancer progression, underscoring their translational significance.

In conclusion, metric-space analysis of cancer PPI networks represents a powerful and innovative approach for rational drug discovery. By highlighting conserved network structures and central functional hubs, this framework facilitates the identification of promising therapeutic targets across diverse cancer types.

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Author Contributions

The author solely contributed to all aspects of the study, including conceptualization, data curation, formal analysis, investigation, methodology, software, writing – original draft, and writing – review & editing.

Competing Interests

The authors declare that there is no competing interest exist.

AI-Assisted Technologies Statement

I confirm that I used ChatGPT only for the purpose of basic grammar correction and language enhancement during the preparation of this manuscript. All AI-assisted text has been carefully reviewed and edited by me for accuracy. I take full responsibility for the content of the manuscript.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: FDR corrected enrichment analysis.
2. Table S2: Top pathway functions of breast cancer.
3. Table S3: Top pathway functions of pituitary cancer.
4. Table S4: Top pathway functions of lung cancer.
5. Table S5: Top pathway functions of kidney cancer.
6. Table S6: Top pathway functions of liver cancer.
7. Table S7: Top pathway functions of cervix cancer.
8. Table S8: Top pathway functions of ovary cancer.
9. Table S9: Top pathway functions of fallopian cancer.
10. Table S10: Top pathway functions of endometrium cancer.
11. Table S11: Top pathway functions of pancreas cancer.
12. Table S12: Top pathway functions of glioblastoma cancer.
13. Table S13: Top pathway functions of glioma cancer.
14. Table S14: Top pathway functions of rectum cancer.
15. Table S15: Summary of functional pathways in zones of breast cancer.
16. Table S16: Summary of functional pathways in zones of pituitary cancer.
17. Table S17: Summary of functional pathways in zones of kidney cancer.
18. Table S18: Summary of functional pathways in zones of liver cancer.
19. Table S19: Summary of functional pathways in zones of pancreas cancer.
20. Table S20: Summary of functional pathways in zones of cervix cancer.
21. Table S21: Summary of functional pathways in zones of ovary cancer.
22. Table S22: Summary of functional pathways in zones of glioblastoma cancer.
23. Table S23: Summary of functional pathways in zones of glioma cancer.
24. Table S24: Summary of functional pathways in zones of fallopian cancer.
25. Table S25: Summary of functional pathways in zones of fallopian cancer.
26. Table S26: Summary of functional pathways in zones of endometrium cancer.
27. Table S27: Summary of functional pathways in zones of rectum cancer.
28. Table S28: Distribution of essential proteins in zones of cancer PINs.
29. Table S29: Distribution of signalling proteins in zones of cancer PINs.
30. Table S30: Distribution of growth proteins in zones of cancer PINs.
31. Table S31: Distribution of cell cycle proteins in zones of cancer PINs.
32. Table S32: Distribution of drug target proteins in zones of cancer PINs.
33. Table S33: Distribution of oncogene proteins in zones of cancer PINs.
34. Table S34: Distribution of suppressors proteins in zones of cancer PINs.

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