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Ranking cancer pathways at the core of the protein interaction network: Identifying key signaling protein using the odds ratio test

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Abstract

Understanding the intricate network of cancer pathways within protein-protein interactions (PPIs) presents a considerable challenge. Ranking these pathways by importance is difficult, as their relevance varies depending on cancer type and specific biological context. In this study, a probability odds ratio (OR) test was employed to uncover significant insights into this complexity. PPI networks were analyzed as a metric space to gain insights into their organization and functional architecture. A central protein was identified as the network's "center," with other proteins grouped into specific zones according to their proximity to this central point. The analysis focused on the central zones of the network, examining pathways for functional enrichment, investigating molecular mechanisms linked to oncogenes and tumor suppressors, and identifying critical proteins involved in key cellular processes. The findings highlight the importance of central proteins and pathways in driving oncogenesis and offer potential therapeutic targets. The analysis revealed an enrichment of cancer-related pathways, including PI3K-AKT, TNF, JAK-STAT, mTOR, and Wnt, with central zones of the interaction network demonstrating an important role in cancer progression. Zones 1 and 2 showed a dense concentration of cancer-associated pathways, highlighting the critical roles of core proteins in signaling and functional interactions essential to tumor biology. Among the pathways, the PI3K-AKT pathway was dominant in zone 1, accounting for approximately 51% of signaling proteins. The TNF pathway exhibited a distinct pattern, with an OR of 4.22, indicating its higher concentration in zone 1 compared to zone 2. In contrast, pathways such as JAK-STAT, mTOR, and Wnt showed more stable distributions across zones but exhibited slightly lower ORs. Importantly, ten proteins emerged as key players, central to multiple pathways and crucial for cancer progression, cell survival, and metabolism. These proteins – PRKCA, SOS2, AKT1, PIK3CA, AKT2, AKT3, PIK3CB, PIK3CD, PIK3R2, and PIK3R3 – are closely associated with oncogenic processes. Each contributes to cell proliferation, survival, and differentiation, with functional implications across various cancer types, including lung cancer. Understanding the roles of these proteins within the broader cancer pathway network deepens knowledge of tumor biology and opens new possibilities for the development of novel therapeutic approaches.

Keywords: Cancer pathways; Protein interaction networks; Therapeutic targets; Odds ratio analysis; Lung cancer progression; PI3K-AKT signaling

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1. Introduction

The ambiguous relationship between cancer and protein-protein interactions (PPIs) has been a focus of biomedical research for decades, as understanding this relationship is crucial for identifying key drivers of cancer progression and potential therapeutic targets.[1] In recent years, the development of high-throughput techniques has significantly enhanced the ability to map human protein- PPI networks (PPINs), offering insights into the molecular underpinnings of cancer.[2] PPIs constitute an extensive network of molecular interactions that play essential roles in maintaining cellular homeostasis, regulating gene expression, and facilitating cellular responses to environmental signals.[3] Aberrations in these interactions often contribute to the uncontrolled proliferation and apoptosis evasion characteristic of cancerous cells.[4] A critical aspect of understanding cancer biology involves the identification of key signaling proteins within these networks, as they serve as potential biomarkers for early detection and therapeutic targets.[5]

The human PPIN is an intricate system comprising thousands of proteins that interact with each other to regulate cellular functions such as signaling, growth, metabolism, and immune response.[6] Protein interactions are fundamental to cellular decision-making processes that control key events like proliferation, differentiation, and survival. Dysregulation of these networks can lead to cancer development, progression, and metastasis.[7] Understanding how proteins interact within this complex network and identifying central nodes – proteins that are highly interconnected or pivotal in signal transduction – can provide insights into the molecular mechanisms driving cancer.[8] These central nodes, often termed "master regulators," influence essential cellular processes by regulating the expression of numerous target genes. A central hypothesis in cancer research is that master regulators serve as promising targets for drug development, given their involvement in multiple aspects of cancer biology, including cell cycle regulation, apoptosis, and DNA repair.[9]

Within the PPIN, several signaling pathways have emerged as critical regulators of cancer progression. Key pathways such as PI3K-AKT, mTOR, Wnt, and JAK-STAT play fundamental roles in regulating cell proliferation, survival, metabolism, and invasion, all of which are hallmark features of cancer cells.[10-13] Dysregulation of these pathways is often implicated in tumorigenesis, making them prime targets for therapeutic intervention.[14] For instance, the PI3K-AKT pathway is frequently activated in many cancers and is associated with poor prognosis, highlighting its potential as a target for precision therapies.[15] Similarly, the Wnt signaling pathway, which regulates stem cell maintenance and differentiation, has been linked to cancer metastasis and drug resistance when aberrantly activated.[16] The identification of critical proteins within these pathways can pave the way for the development of novel targeted therapies that can effectively disrupt oncogenic signaling and inhibit cancer cell survival and proliferation.

One of the most promising approaches in cancer research is the integration of PPINs with high-throughput data, allowing for a comprehensive understanding of how protein interactions regulate cellular processes in both healthy and diseased.[17] Advanced techniques such as affinity purification coupled with mass spectrometry and yeast two-hybrid screening have enabled the identification of novel PPIs.[18] In addition, network-based approaches, including graph theory and statistical tools, are increasingly being employed to analyze the structural and functional properties of these networks. Such approaches enable the identification of protein modules or clusters of proteins that are tightly interconnected and may function together within the same cellular process or pathway. Uncovering these modules can lead to the discovery of novel drug targets and biomarkers, advancing cancer diagnosis and prediction.

A powerful tool in network analysis is the odds ratio (OR) test, which provides a robust statistical framework for assessing the enrichment of differentially, expressed proteins within specific pathways or protein modules. The OR test quantifies the strength of association between a given protein and a cancer-related pathway, allowing researchers to prioritize proteins based on their likelihood of involvement in cancer progression. By combining the OR test with network analysis, cancer pathways can be ranked according to their relevance to tumorigenesis, highlighting those most likely to contain key signaling proteins. This approach allows for a more focused and systematic investigation of cancer-related pathways, providing a clear roadmap for further experimental validation.

The primary aim of this study is to identify key signaling proteins that play crucial roles in cancer progression by ranking cancer pathways within the core of the protein interaction network using the OR test. By focusing on the central nodes within the PPIN, a deeper understanding of the essential signaling pathways that drive cancer biology is expected to be achieved. The OR test serves as a guiding framework to prioritize these pathways, enabling the discovery of novel cancer-related proteins that may function as biomarkers or therapeutic targets. This approach offers a comprehensive framework for identifying critical components within the cancer network,

facilitating the discovery of new treatment strategies, and the development of targeted therapies aimed at disrupting the aberrant signaling events that sustain tumor growth.

In summary, understanding the complex network of PPIs and their roles in cancer is crucial for advancing knowledge of tumor biology and developing more effective cancer treatments. Advanced network analysis techniques and statistical methods, such as the OR test, enable the identification of key proteins and pathways integral to cancer progression. While enhancing our understanding of the molecular mechanisms driving cancer, findings from such studies will provide critical insights into cancer diagnosis, prognosis, and treatment, which are crucial for the development of more personalized and targeted therapies for patients.[19]

2. Materials and methods

2.1. Distance-based mapping of PPINs

The PPINs were treated as a map, where proteins represent points and their interactions form paths. A Python tool, built on the C++ BOOST library (http://www.boost.org/), was utilized to calculate the shortest "travel" distances between all protein pairs. The protein or proteins with the least total "travel" distances to all others were identified as the network's central point(s), similar to the center of a city. Proteins were then ranked based on their distance from this central point, effectively dividing the network into zones, analogous to how neighborhoods are arranged by their proximity to a city's center.

This map-based approach enabled the identification of central point(s) and the grouping of remaining proteins into zones based on their proximity to the center. The step size represents the number of connections or transitions from the central point(s) to each protein in the network. For instance, zone 1 comprises proteins that one step away from the center, while zone 2 includes proteins two steps away, and so on. To aid in understanding, Figure 1 is proposed to visually represent these zones and step sizes, clearly illustrating the distribution of proteins across different distances from the center.

By conceptualizing protein interactions as distances in a metric space, a distinct pattern emerged – a dense core surrounded by progressively sparser "shells." This tiered organization demonstrated biological relevance, highlighting the effectiveness of distance-based analysis in distinguishing healthy and diseased networks. Notably, proteins located at the center, particularly sensory proteins, stood out as potential therapeutic targets. These "core zones" in human networks were enriched with essential proteins and established drug targets, further supporting the approach's potential for identifying novel drug candidates.

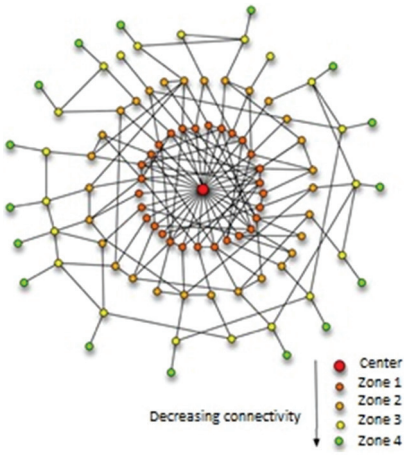


Figure 1. Visual representation of the PPIN, with proteins grouped into zones based on their distance from the central point(s). The central point(s) are identified as proteins with the shortest total travel distance to all others. Proteins are ranked and categorized into zones (zone 1, zone 2, zone 3, and zone 4) based on their step size, defined as the number of connections from the central point(s).
Abbreviation: PPIN: Protein-protein interaction network.

2.2. Pathway analysis and enhancement of functionality investigation

To evaluate the biological relevance of specific zones within the PPIs, proteins were categorized according to their proximity to the network's center. Pathway enrichment analysis was conducted for proteins within each zone to identify unique functional characteristics associated with these regions.[20] Tools such as gene set enrichment analysis from comparative toxicogenomic databases and gene ontology term enrichment were employed, with a significance threshold set at 0.01. In addition, the proportion of proteins involved in each enriched signaling pathway was calculated to assess whether the zones displayed specialized functional roles.

2.3. Examination of pathways involving oncogenes and tumor suppressor proteins

The analysis focused on pathways involving oncogenes and tumor suppressor genes. Protein scores were analyzed with particular emphasis on oncogenes and tumor suppressors, utilizing data from cancer genome-wide sequencing studies. Interactions with significant associations were prioritized, revealing that these interactions often involved genes with well-established causal links to cancer.[21]

2.4. Statistical analysis

The statistical package SPSS Statistics 26 (Statistical Package for the Social Sciences, https://www.ibm.come/spss, USA) was utilized to compute the OR and determine the associated confidence interval (CI) to assess whether

cancer pathways were more prevalent in zone 1 compared to zone 2.

In biomedical trials with dichotomous outcomes, effect measures are typically derived by comparing risks or odds between two intervention groups. These comparisons can be expressed as ratios (risk ratio or OR) or as differences in risk (risk difference).

Risk is defined as the probability of a specific event or outcome occurring, calculated as the number of occurrences of the outcome of interest divided by the total number of possible outcomes. The term odds are frequently used interchangeably with risk, though it specifically refers to the ratio of the probability of an event occurring to the probability of it not occurring. Odds and risks can be interconverted using the formula: odds = risk/(1 − risk).[22]

In this study, the odds represent the ratio of the probability of proteins being associated with a specific pathway to the probability of proteins not being associated with that pathway. This is expressed as p/(1−p), where p is the probability of a protein belonging to the pathway, also referred to as the risk.

The OR is a statistical measure used to quantify the strength of association between two events: event A (a protein belonging to a specific pathway) and event B (the protein being located in a particular zone of the network).

3. Results

3.1. Identification of core cancer pathways in the PPIN

Earlier studies employed a distinctive approach involving the calculation of metric space to categorize proteins and allocate them to specific zones based on their proximity to the network's center.[17] In this study, a 9448-protein network was analyzed and segmented into six distinct zones such as 374, 4610, 3464, 578, 14, and 2 proteins, respectively. Enrichment analyses were subsequently performed on these zones using comparative toxicogenomic databases and gene ontology term enrichment analysis, encompassing gene set enrichments.[23] The findings revealed that among the six zones in the network, zone 1 and zone 2 exclusively housed the critical pathways in cancer, including PI3K-AKT, TNF, JAK-STAT, mTOR, and Wnt signaling pathway (Table 1). This observation led to the classification of cancer pathways within the core of the PPIN, aiming to identify key signaling proteins.

3.2. Zonal distribution of cancer-related signaling pathways

3.2.1. Comparison of proteins related to signaling pathways across different zones

The proteins linked to signaling pathways in various zones were examined. A descriptive analysis of protein interactions across various zones revealed that about half of the proteins in each zone are part of the PI3K pathway (Table 2). Conversely, the mTOR pathway has the fewest associated proteins in zone 1, while the TNF pathway is least represented in the zone 2.

3.2.2. Significance of zones in cancer progression

The central zones (zones 1 and 2) are enriched with proteins involved in critical signaling pathways implicated in cancer, including PI3K-AKT, TNF signaling, JAK-STAT, mTOR, and Wnt pathways. These zones act as hubs for signal transduction and functional interactions essential for tumor progression. Zone 1 contains the highest concentration of PI3K-AKT pathway-related proteins (51%), highlighting its role as a central regulator of cell survival and proliferation. Zone 2 shows a lower but remains significantly enriched with cancer pathways, suggesting a secondary role in modulating signaling cascades.

Table 1. Distribution of proteins associated with signaling pathways across different zones

Pathway category	Zone 1 (%)	Zone 2 (%)
PI3K-AKT	68 (18.18)	244 (5.29)
TNF	46 (12.29)	51 (1.10)
JAK-STAT	35 (9.35)	105 (2.27)
mTOR	28 (7.48)	79 (1.71)
Wnt	29 (7.75)	97 (2.10)

Abbreviations: PI3K-AKT: Phosphatidylinositol 3-kinase-protein kinase B; TNF: Tumor necrosis factor; JAK-STAT: Janus kinase-signal transducer and activator of transcription; mTOR: Mammalian target of rapamycin.

Table 2. Descriptive statistics for signaling pathways related proteins within zones

Zone	Number of proteins	Pathway category	*P*	Odds
Zone 1	133	PI3K-AKT	0.51	1.04
		TNF	0.345	0.528
		JAK-STAT	0.26	0.357
		mTOR	0.21	0.266
		Wnt	0.22	0.278
Zone 2	453	PI3K-AKT	0.538	1.167
		TNF	0.11	0.126
		JAK-STAT	0.225	0.29
		mTOR	0.174	0.211
		Wnt	0.214	0.272

Notes: p=belonging probability; Odds = $\frac{p}{1-p}$.

Abbreviations: PI3K-AKT: Phosphatidylinositol 3-kinase-protein kinase B; TNF: Tumor necrosis factor; JAK-STAT: Janus kinase-signal transducer and activator of transcription; mTOR: Mammalian target of rapamycin.

The distinct enrichment patterns across zones reflect the functional hierarchy of the network, with central proteins (zone 1) acting as master regulators, while peripheral proteins in the outer zones contribute to less specialized processes.

3.2.3. Statistical significance of OR values

To assess the probability of specific proteins appearing in a given zone, OR values were calculated based on their distribution across the network (Table 3). The statistical significance of these OR values was determined using 95% CIs, which provide a measure of the precision and reliability.

The TNF pathway exhibited an OR of 4.22 (CI: 2.68 – 6.66), indicating that proteins associated with this pathway are approximately 4 times more likely to be found in zone 1 than in zone 2. The lower bound of the CI (2.68) being well above 1 confirms the statistical significance of this result ($p < 0.05$), underscoring the TNF pathway's central role in the network core and its potential role in cancer progression.

In contrast, pathways such as JAK-STAT (OR: 1.17, CI: 0.756 – 1.83), mTOR (OR: 1.2, CI: 0.74 – 1.94), and Wnt (OR: 1.06, CI: 0.67 – 1.69) had ORs close to 1, with CIs that include 1, suggesting a more even distribution across zones without a statistically significant preference for zone 1. Despite the PI3K-AKT pathway's dominance in zone 1 (51% of signaling proteins), its OR was 0.87 (CI: 0.6 – 1.29), indicating a slightly lower likelihood of being concentrated in zone 1 compared to zone 2, though this result was not statistically significant. These findings highlight the TNF pathway as a statistically significant outlier in zone 1, emphasizing its unique role in the network core. Overall, the TNF pathway stands out as the most significant differentiating factor between the two zones, with its proportion dropping dramatically beyond zone 3 to approximately 10% (Table 2), while other pathways exhibit a more consistent distribution across the zones.

Table 3. ORs and confidence intervals for key cancer-related pathways

Pathway category	OR	Confidence interval	
		Lower	Upper
TNF	4.16	2.62	6.6
JAK-STAT	1.22	0.78	1.91
mTOR	1.26	0.77	2.04
Wnt	1.02	0.64	1.63
PI3K-AKT	0.89	0.61	1.31

Abbreviations: OR: Odds ratio; PI3K-AKT: Phosphatidylinositol 3-kinase-protein kinase B; TNF: Tumor necrosis factor; JAK-STAT: Janus kinase-signal transducer and activator of transcription; mTOR: Mammalian target of rapamycin.

The spatial distribution of pathways across zones provides insights into their functional roles. For instance, the significant enrichment of the TNF pathway in zone 1 (OR = 4.22) indicates its central role in inflammatory responses linked to cancer. The PI3K-AKT pathway, while dominant in zone 1, extends into outer zones, suggesting its involvement in both core and peripheral signaling processes. In contrast, JAK-STAT, mTOR, and Wnt pathways show relatively more stable distributions, suggesting their complementary roles in cancer progression.

In summary, the analysis suggests that, in most cases, the probability of a protein belonging to a cancer-related pathway is greater in zone 1 than in zone 2. If these pathways are particularly relevant to cancer research, the findings indicate that proteins within zone 1 are more likely to be associated with key oncogenic processes.

3.3. Key proteins driving cancer-related signaling pathways

3.3.1. The ten most significant proteins in signaling pathways across various zones

To determine the proteins involved in the greatest number of pathways, the top ten were selected. Each of these proteins is present in at least three pathways, with all being part of the PI3K and mTOR pathways (Table 4). A value of

Table 4. Distribution of ten most significant proteins in signaling pathways within zones

Name of protein	PI3K-AKT	TNF	JAK-STAT	mTOR	Wnt	Average (%)
PRKCA	1	0	0	1	1	60
SOS2	1	0	1	1	0	60
AKT1	1	1	1	1	1	80
PIK3CA	1	1	1	1	0	80
AKT2	1	1	1	1	0	80
AKT3	1	1	1	1	0	80
PIK3CB	1	1	1	1	0	80
PIK3CD	1	1	1	1	0	80
PIK3R2	1	1	1	1	0	80
PIK3R3	1	1	1	1	0	80

Abbreviations: PRKCA: Protein kinase C alpha; SOS2: Son of sevenless homolog 2; AKT1: AKT serine/threonine kinase 1; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; AKT2: AKT serine/threonine kinase 2; AKT3: AKT serine/threonine kinase 3; PI3KCB: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta; PI3KCD: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta; PIK3R2: Phosphoinositide-3-kinase regulatory subunit 2; PIK3R3: Phosphoinositide-3-kinase regulatory subunit 3; PI3K-AKT: Phosphatidylinositol 3-kinase-protein kinase B; TNF: Tumor necrosis factor; JAK-STAT: Janus kinase-signal transducer and activator of transcription; mTOR: Mammalian target of rapamycin.

one indicates the protein's inclusion in the pathway, while 0 indicates its absence.

4. Discussion

This study provides a comprehensive understanding of the centrality of cancer signaling pathways within large PPINs, comprising 9448 proteins organized into six distinct zones based on their proximity to the network center. Analysis of the innermost zones (zones 1 and 2) uncovered a significant enrichment of cancer-related signaling pathways, including PI3K-AKT, TNF signaling, JAK-STAT, mTOR, and Wnt pathways. These findings highlight the critical roles of central proteins in oncogenic processes and offer valuable insights into cancer biology.

Zones 1 and 2, collectively representing the network's core, exhibit a dense concentration of cancer-associated pathways. Proteins in these zones likely serve as key hubs for signal transduction, underscoring their importance in tumor progression and survival. Notably, the PI3K-AKT pathway accounts for 51% of signaling proteins in zone 1, highlighting its central role in regulating cancer cell survival and proliferation. This high representation suggests a direct correlation between pathway centrality and functional significance in oncogenesis.

In contrast, the TNF pathway displays a pronounced preference for zone 1, with an OR of 4.22, indicating a significantly higher likelihood of being localized in the network core. This aligns with TNF's well-established role in modulating inflammatory responses that are intricately linked to cancer progression.[24] The distinct enrichment patterns of these pathways suggest a functional classification within the network, where certain pathways are more central to core biological processes like survival, while others contribute to peripheral signaling roles.[25] Targeting TNF signaling could disrupt multiple oncogenic processes simultaneously, making it a promising therapeutic strategy.

Interestingly, while the PI3K-AKT pathway shows a slightly lower probability (OR: 0.87) of zone 1 association, it remains a dominant regulator across zones. Other pathways, such as JAK-STAT, mTOR, and Wnt pathways, show only slight variations between zones, with OR values close to 1. However, the pronounced presence of the TNF pathway in zone 1 strengthens its role in cancer progression and cell survival.[26] In addition, Alpelisib, a PI3Kα inhibitor, has shown significant efficacy in treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations. Clinical trials demonstrated that combining alpelisib with fulvestrant improves progression-free survival in patients with PIK3CA-mutated advanced breast cancer.[27] The identification of PIK3CA as a central protein in zone 1 aligns with these findings, suggesting that targeting PI3K-AKT signaling in the network core could yield similar benefits in other cancers, such as lung cancer. Furthermore, TNF inhibitors, such as infliximab and etanercept, are widely used to treat inflammatory conditions like rheumatoid arthritis and Crohn's disease. Emerging evidence suggests that these agents may also have anti-cancer effects, particularly in cancers driven by chronic inflammation. For instance, preclinical studies have shown that TNF inhibition can suppress tumor growth and metastasis in models of lung cancer.[28] The findings in this study highlight the potential of targeting TNF signaling in the network core to disrupt inflammatory responses that fuel cancer progression.

The identification of ten highly influential proteins, predominantly involved in PI3K-AKT and mTOR signaling, underscores a convergence of critical pathways that sustain cancer cell viability. Proteins like AKT serine/threonine kinase 1 (AKT1), PIK3CA, and protein kinase C alpha (PRKCA) exemplify master regulators whose dysregulation drives key oncogenic processes, including cell survival, metabolic reprogramming, and resistance to apoptosis. Specifically, mutations or overactivation of these proteins are frequently observed in various cancers, including lung cancer, highlighting their therapeutic potential.[29] Son of sevenless homolog 2 (SOS2) is involved in the Ras signaling pathway, which is crucial for cell growth and survival, and its dysregulation can contribute to tumorigenesis.[30] AKT1 is a critical regulator of cell survival and growth, frequently activated in cancer cells, contributing to oncogenesis and resistance to apoptosis.[31] PIK3CA, a key component of the PI3K-AKT pathway, regulates cell growth, proliferation, and survival, with mutations frequently observed in cancers.[32] AKT serine/threonine kinase 2 (AKT2) has a role in glucose metabolism, cell proliferation, and survival, with its overactivation implicated in cancer, particularly in metastasis and resistance to chemotherapy.[33,34] AKT serine/threonine kinase 3 (AKT3) has been shown to contribute to cell survival and cancer progression, with distinct roles in brain and lung cancers.[31] Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB) supports cell growth and survival by activating the PI3K-AKT pathway and is linked to tumorigenesis and metastasis in several cancers, including lung cancer.[35] Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PIK3CD) is involved in immune cell function and also plays a role in cancer, particularly in B-cell malignancies and lung cancer.[36] Phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2), a regulatory subunit in the PI3K pathway, is linked to cancer cell proliferation, survival, and migration.[37] Phosphoinositide-3-kinase

regulatory subunit 3 (PIK3R3) regulates PI3K activity and is associated with tumorigenesis, particularly in breast and lung cancers.[38]

The distinct enrichment of pathways across zones also provides insights into the hierarchical organization of the PPI network. Proteins in zone 1 function as central nodes, facilitating critical interactions, whereas proteins in the outer zones may have more redundant functions. This spatial distribution aligns with the concept of "core-periphery" structure in biological networks, where central (core) nodes integrate diverse signals, and peripheral nodes contribute to specific processes.[39]

Moreover, the slight variations in ORs for pathways like JAK-STAT, mTOR, and Wnt across zones suggest subtle roles in different stages of cancer progression. These pathways may represent complementary therapeutic targets, and their inhibition, when combined with central pathway inhibitors, could produce synergistic therapeutic effects.

This study lays the foundation for integrating network centrality metrics with functional annotations to refine drug discovery strategies. Prioritizing pathways and proteins based on their network centrality and enrichment can simplify the identification of viable therapeutic targets.

Finally, the enrichment of critical cancer pathways and key signaling proteins within the network core highlights their fundamental roles in tumor biology. These findings not only deepen the understanding of cancer progression but also pave the way for developing targeted therapies aimed at disrupting central signaling hubs.

5. Conclusion

This study maps a path through the complexity of cancer-related protein interaction networks, uncovering key insights into pathway enrichment and functional importance within the core zones of the network. Using the OR test, cancer-centric pathways, such as PI3K-AKT, TNF, JAK-STAT, mTOR, and Wnt, were identified with the highest concentrations in zones 1 and 2, where signaling proteins crucial to tumor progression are densely clustered. The PI3K-AKT pathway, particularly dominant in zone 1, emerged as a critical driver, constituting over half of the core signaling proteins. Meanwhile, the TNF pathway displayed a uniquely high OR, highlighting its role in inflammation and its link to cancer.

This analysis identifies ten pivotal proteins (PRKCA, SOS2, AKT1, PIK3CA, AKT2, AKT3, PIK3CB, PIK3CD, PIK3R2, and PIK3R3) positioned at the intersection of key pathways, with broad implications for cell proliferation, survival, and differentiation. These proteins not only play vital roles in oncogenic processes but also represent promising targets for therapeutic intervention, particularly in lung cancer.

The identification of key signaling proteins and pathways within the core of the protein interaction network provides a strong foundation for further investigation. Future studies will focus on experimentally validating the biological functions and roles of these ten identified proteins in cancer progression through both *in vitro* and *in vivo* models, assessing their impact on cell proliferation, survival, and metastasis. In addition, efforts will be directed toward developing biomarkers for early cancer detection and personalized therapeutic strategies based on the identified signaling proteins and pathways.

The findings from this study offer a strategic framework for targeted therapies, emphasizing the potential to disrupt cancer progression by targeting central signaling hubs. By refining the understanding of pathway interactions and protein roles, this study paves the way for advancements in cancer treatment strategies.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: Emad Fadhal
Data curation: Emad Fadhal
Formal analysis: All authors
Investigation: All authors
Methodology: All authors
Writing – original draft: All authors
Writing – review & editing: Emad Fadhal

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data supporting the findings of this study are available from the corresponding author on reasonable request.

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