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The Significance of Key Proteins in the RAS Signaling Pathway: Implications for Cancer and Therapeutic Targets

Emad Fadhal *

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

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

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Abstract

The RAS signaling pathway is a crucial cell transduction pathway central to transmitting signals from outside the cell to the cell nucleus and influencing fundamental biological mechanisms like cell growth, division, and specialization. This signaling pathway has recently received much attention in scientific research because of its involvement in various diseases, especially carcinogenesis. Our study identified the significance of crucial proteins in the RAS signaling cascade in cancer development and progression. We found that proteins such as PDGFRB, PDGFB, IGF1, HRAS, HGF, FGF10, and ABL1 are involved in various types of cancer and could serve as potential therapeutic targets. Misregulation of these proteins may result in unregulated cell proliferation and contribute to cancer development and maintenance. The study also emphasizes the importance of oncogenes in cancer development, with RAS being identified as a pivotal oncogene. In addition, the findings indicate several proteins, including PDGFRA, NRAS, HRAS, CSF1R, KIT, MET, ABL1, FGFR2, FGFR3, and KRAS, function as oncogenes and are related to different forms of cancer and diseases. Targeted therapies for these proteins are being investigated in various cancer types, including gastrointestinal stromal tumors, chronic myelogenous leukemia, and bladder cancer. Moreover, we identified NF1 as a critical tumor suppressor gene essential in regulating cellular proliferation. Mutations in the

NF1 gene lead to neurofibromatosis category 1. This paper emphasizes the significance of crucial proteins implicated in the RAS signaling pathway in cancer growth and advancement. Understanding the complexity of these proteins and their dysregulation could offer essential insights into the progression of practical treatment approaches that enhance and refine cancer therapies. These findings provide promising avenues for further research and advances in cancer treatment and give us hope for better outcomes in the fight against this challenging disease.

Keywords
RAS signaling pathway; oncogenes; suppressor gene; diseases; cancer development

1. Introduction

The RAS signaling pathway, a critical component of cell communication, has been a significant research focus due to its influence on fundamental cellular processes like development, proliferation, and differentiation [1]. A landmark discovery by Hanahan et al. identified RAS as an oncogene, highlighting its role in cancer initiation [2]. Further studies have revealed the intricate regulation of RAS signaling involving feedback loops and complex interactions between proteins [3]. Recent advancements have shed light on RAS involvement in various diseases. For instance, Prior et al. demonstrated its dysregulation in cardiovascular disease, emphasizing the need for targeted therapies [4]. Additionally, the pathway has become a promising target for cancer treatment. A clinical trial by Morris et al. showcased the efficacy of novel RAS inhibitors against advanced pancreatic cancer, paving the way for future therapeutics [5].

Beyond RAS itself, research has delved into specific proteins within the pathway and related pathways for their therapeutic potential in cancer. Heldin explored the role of PDGFR family members, particularly PDGFRB, in cancer progression and their potential as therapeutic targets [6]. Similarly, Martinko et al. investigated targeting upregulated cell surface proteins in HRAS-driven cancers [7]. Gherardi et al. focused on the HGF-MET signaling pathway and advancements in MET-targeted therapies [8]. Due to its frequent overexpression, Pian et al. explored targeting the IGF1R pathway in breast cancer [9]. Studies by [10-12] further suggest FGF10, ABL kinase, and other proteins as potential therapeutic targets due to their roles in cancer progression.

In conclusion, the RAS signaling pathway is central to cell biology and medicine. Ongoing research unveils its intricate regulation and therapeutic potential, making it an attractive target for further investigation. This study aims to identify critical proteins within the RAS pathway and elucidate their contributions to cancer development and progression. By understanding these proteins, we can gain valuable insights into cancer biology and pave the way for developing more effective cancer therapies.

2. Materials and Methods

Our preceding study employed a particular method to study protein-protein interactions (PPIs). We regarded these interactions within a metric space framework and subjected them to analysis using graph theory tools [13]. In this approach, we represented all the PPIs as a metric space and

determined the central points in every network. Categorizing the leftover proteins into distinct 'zones' was determined by their network-based distance at these central points. For instance, zone one included proteins within one move from the central point, whereas zone two consisted of proteins two moves away.

Our findings revealed that proteins engaged in radial interactions through this central point, exhibiting a dense concentration at the network's core and diminishing levels as we extended away from the center. The arrangement of proteins from the central point to distinct hierarchies was identified as biologically significant. As a result, we deduced that assessing PPIs within a metric space, particularly considering zones relative to the center, can unveil pivotal distinctions between PPI networks observed in healthy and pathological tissues. Following the methodology outlined in our prior research, our continuing investigation proposes that core zones within specific human protein interaction networks exhibit a noteworthy enrichment of essential proteins and recognized drug targets [14-17].

In the current study, we specifically concentrated on zone two, the largest interconnected zone abundant with proteins related to diverse molecular functions.

2.1 Pathway Analysis and Enhancement of Functionality Investigation

Proteins were grouped according to their distance from the center to assess the biological significance of specific zones in the PPIs. We performed an overrepresented pathway analysis for groups of proteins linked to each zone. This analysis helped identify specific features attributed to these zones. Diverse web services were employed to conduct zone enrichment analysis; encompassing gene set enrichers for comparative toxicogenomics databases and gene ontology term enrichment analysis. A significance level of 0.01 was used for determination. Finally, the ratio of proteins implicated in every enriched signaling pathway was calculated to determine whether the zones exhibited specialized functionality.

2.2 Examination of Pathways Involving Oncogenes and Tumor Suppressor Proteins

The protein scores were evaluated with special consideration given to the values observed in oncogenes and tumor suppressors. Data from cancer genome-wide sequencing studies were utilized to identify enhanced signaling pathways. Precisely, emphasis was placed during analysis interactions on significant levels. The findings exposed that these interactions frequently implicated genes with causal associations to cancer [18].

2.3 Crucial Proteins Involved in Cellular Functions, Signaling Pathways, Growth Mechanisms, Regulation of the Cell Cycle, and Having Potential as Targets for Therapeutic

To assess zone two within the PPIs, we utilized a collection of essential human proteins derived from the corresponding gene knock-out phenotypes observed in mice [19, 20]

3. Results

Recently, there has been a widespread acknowledgment of the significance of PPI in unraveling cellular functions and pinpointing potential therapeutic targets. Our previous study [13] revealed that the relationships between human proteins can be articulated as a metric space. These spaces

group proteins into zones according to their closeness to hub proteins that play essential roles in biological networks. A subsequent study found that the zone closest to the network center contains essential proteins specialized for basic functions [14]. This observation supports the hypothesis that our approach could be valuable for drug target discovery. We suggested that proteins in the central position, particularly those engaged in sensory functions, could be potential targets for therapeutic intervention. Furthermore, we identified proteins near the network center as potential targets for therapeutic intervention [15-17]. Based on previous analyses, our current investigation focused on zone two, abundant in proteins linked to diverse cellular processes. Zone 2 is the most highly interconnected. We analyzed the participation of 4,495 proteins located in zone 2 in various signaling pathways associated with the RAS pathway by mapping them to the KEGG pathway database [21] (Figure 1).

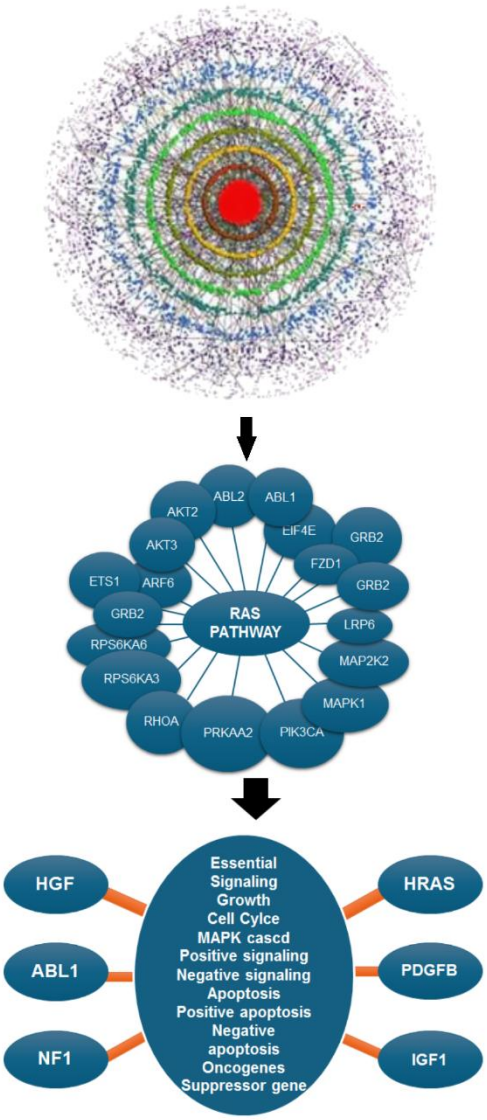

Figure 1 The workflow for selecting the final set of genes.

3.1 The Distribution of Proteins Related to Essential Signalling, Growth Mechanisms, Regulation of the Cell Cycle, MAPK Cascade, On Signalling, and Off Signalling within Zone 2 of the RAS Signaling Pathway

The initiation and control of signaling pathways are crucial in vital participation in the advancement and evolution of cancer. Successful targeting of cancer cell signaling pathways is often hampered by alterations or dysregulations within these pathways that promote uncontrolled growth and viability of cancer cells. Disruption of these signaling pathways can impair their ability to support cancer growth [22-25]. According to (Table 1), signaling proteins accounted for the most significant proportion of 87%, highlighting the importance of signaling proteins over other functions. Essential proteins follow it at 33.3%. The remaining functions are expressed in the following ratios: MAPK cascade (30.7%), positive signal (26.9%), cell cycle (7.6%), negative signal (7.6%), and proliferation (2.3%).

Table 1 The distribution of proteins related to essential functions, signaling, growth mechanisms, cell cycle regulation, MAPK cascade, on signaling, and off signaling within zone 2 of the RAS signaling pathway.

Pathway	# of proteins	Essential	Signalling	Growth	Cell cycle	MAPK cascade	Positive signalling	Negative signalling
RAS signaling pathway	156	52 (33.3%)	136 (87%)	7 (2.3%)	12 (7.6%)	48 (30.7%)	42 (26.9%)	12 (7.6%)

3.2 Cellular Regulation and Therapeutic Target in Proteins Related to the RAS Signaling Pathway within Zone 2

Proteins contribute significantly to the dynamics of cancer networks, functioning as both cancer-promoting oncogenes and cancer-preventing tumor suppressor genes. Their interactions strongly influence cancer cell behavior [26, 27]. Notably, 8.9% of proteins were identified as successful therapeutic targets, and 6.4% were found to function as oncogenes. This underscores the importance of specific zones with high concentrations of proteins, some of which may be potential drug targets. Other functions of the protein in this context include tumor suppression (0.6%), no involvement in apoptosis (0%), negative regulation of apoptosis (0%), and no positive effect on apoptosis. as shown in Table 2.

Table 2 The distribution of proteins related to cellular regulation and therapeutic target within zone two of the RAS signaling pathway.

Pathway	# of proteins	Apoptosis	Positive apoptosis	Negative apoptosis	Oncogenes	Suppressor gene	successful target protein
RAS signaling pathway	156	0 (0.00%)	0 (0.00%)	0 (0.00%)	10 (6.4%)	1 (0.6%)	14 (8.9%)

3.3 Important Proteins Implicated in Cancer Progression are Identified to Congregate within the Signaling Pathways of the RAS Pathway

Several vital proteins in the RAS cascade contribute significantly to cancer development. The RAS cascade is a complex network in cell growth, proliferation, and survival. Here, we present some critical proteins involved in RAS signaling and their importance in cancer (Table 3). PDGFRB contributes to cell proliferation, differentiation, and survival. It was implicated in various cancers, including gastrointestinal stromal tumors (GISTs) and some types of leukemia. Targeting PDGFRB has been explored as a potential therapeutic strategy in these cancers [28].

Table 3 The distribution of essential signalling, growth, cell cycle, negative signaling, oncogenes, and a tumor suppressor in RAS signalling pathway-related proteins in zone two.

Common proteins	Essential	Signalling	Growth	Cell cycle	MAPK cascade	Positive signaling	Negative signaling	Apoptosis	Positive apoptosis	Negative apoptosis	Oncogenes	Suppressor gene	Successful Target
PDGFRB	✓	✓	×	✓	✓	✓	×	×	×	×	×	×	×
PDGFB	✓	✓	✓	✓	✓	✓	×	×	×	×	×	×	×
IGF1	✓	✓	×	✓	✓	✓	×	×	×	×	×	×	×
HRAS	✓	✓	×	✓	✓	✓	×	×	×	×	✓	×	×
HGF	✓	✓	×	✓	✓	×	×	×	×	×	×	×	×
FGF10	✓	✓	×	✓	✓	✓	×	×	×	×	×	×	×
ABL1	✓	✓	×	✓	×	×	×	×	×	×	✓	×	×
NF1	✓	✓	×	×	✓	×	✓	×	×	×	×	✓	×

Furthermore, PDGFB is a ligand that binds to PDGFRB and activates its signaling pathway. Dysregulation of PDGFB/PDGFRB signaling has been observed in several cancers, promoting tumor growth and angiogenesis. Inhibition of this pathway is being investigated as a potential therapeutic approach [29]. In addition, IGF1 is a growth factor that controls cell growth, proliferation, and survival. It contributes significantly to normal development and is involved in cancer development and progression. Elevated IGF1 levels have been linked to an elevated likelihood of specific cancers, such as breast, prostate, and colorectal cancer [30]. HRAS is an oncogene part of the RAS family of GTPases. Mutations in HRAS can lead to its constitutive activation, driving uncontrolled cell proliferation and contributing to cancer development. HRAS mutations manifest in various cancer types, such as bladder and thyroid cancers.

Additionally, HGF is a growth factor that activates the MET receptor tyrosine kinase, engaging in crucial cellular processes like motility, invasion, and metastasis. The dysregulation of HGF/MET signaling is closely linked to cancer progression and metastasis [31]. Furthermore, FGF10, another growth factor, regulates cell proliferation and differentiation, participating in tissue development and repair. Dysregulation of FGF10 has been associated with lung cancer and other malignancies [32]. Lastly, ABL1, a non-receptor tyrosine kinase, significantly contributes to cell signaling and cytoskeleton regulation. The ABL1 gene is notable for its fusion with the BCR gene in the Philadelphia chromosome, resulting in the formation of the BCR-ABL fusion gene. This gene fusion is a distinctive feature of chronic myeloid leukemia (CML) and is targeted by specific therapies, such as tyrosine kinase inhibitors [33].

4. Discussion

Our results show critical proteins' significance in the RAS signaling pathway in cancer development and progression. The RAS pathway is a complex cell growth, proliferation, and survival network. We show the presented proteins, such as PDGFRB, PDGFB, IGF1, HRAS, HGF, FGF10, and ABL1, are implicated in various cancers and may represent potential therapeutic targets. PDGFRB is involved in cell proliferation, differentiation, and existence. Exploring it as a potential therapeutic strategy in cancers such as GISTs and leukemia has been investigated. Dysregulation of PDGFB/PDGFRB signaling is associated with tumor growth and angiogenesis, making it a candidate for inhibition as a therapeutic approach. In addition, IGF1, a growth factor, regulates cell growth, proliferation, and survival, and elevated IGF1 levels are linked to a heightened risk of specific cancers, including breast, prostate, and colorectal cancer.

Further, HRAS, an oncogene, is a part of the RAS family of GTPases. Changes in the genetic code of HRAS lead to its constitutive activation, driving uncontrolled cell proliferation, and are found in various cancers, including bladder and thyroid cancer. Furthermore, HGF is a proliferation factor that activates the MET kinase, which is involved in cell motility, infiltration, and spread. Dysregulation of HGF/MET signaling contributes significantly to the development of cancer. Moreover, FGF10 is a growth factor in cell proliferation and differentiation and is implicated in lung cancer and other malignancies. Finally, ABL1 operates as a tyrosine kinase without a receptor in cell signaling and cytoskeleton regulation.

Oncogenes are pivotal contributors to the initiation and advancement of cancer. These genes participate in promoting cellular proliferation, survival, and division. Mutated or dysregulated, it can lead to uncontrolled cell proliferation and contribute to the initiation and maintenance of cancer.

Several landmark studies and research papers have established the importance of oncogenes in cancer. Many studies unveiled the identification of RAS as an oncogene, highlighting its significance in cancer development [34-38]. Our results identify proteins that act as oncogenes, including PDGFRA, NRAS, HRAS, CSF1R, KIT, MET, ABL1, FGFR2, FGFR3, and KRAS, which are essential critical proteins in various cellular processes and are often associated with different types of cancer and other diseases. Some of these proteins relate to existing targeted therapies or potential therapeutic strategies. However, we can provide general information about the relationship between these critical proteins and targeted therapies or potential therapeutic strategies. PDGFRA mutations in gastrointestinal stromal tumors (GISTs) and targeted therapies like Imatinib and Sunitinib [39]. CSF1R and targeted therapies like Emactuzumab in breast cancer and glioblastoma [40]. KIT mutations in GISTs and targeted therapies like Imatinib [41]. MET dysregulation and targeted therapies that inhibit MET, such as Crizotinib, were being investigated in clinical trials. BCR-ABL1 fusion gene in chronic myeloid leukemia (CML) and targeted therapies like Imatinib, Dasatinib, and Nilotinib [42]. FGFR alterations in bladder cancer and targeted therapies like Erdafitinib and Balversa [43].

Our study identifies NF1 as a crucial tumor suppressor gene in regulating cellular proliferation. Mutations in the NF1 gene lead to neurofibromatosis category 1 (NF1), an inherited condition that makes susceptible individuals to the establishment of benign tumors called neurofibromas, as well as other complications. However, there have been significant advancements in understanding the molecular mechanisms underlying NF1 and the development of potential therapeutic strategies [44-48].

Although specific experimental data is not presented in this context, it is essential to emphasize that identifying these proteins is substantiated by a wealth of literature and prior research in the field [49-52].

Overall, the presented proteins in the RAS signaling pathway offer potential avenues for targeted therapeutic strategies in various cancers. These results emphasize the significance of understanding the complex roles of these proteins in cancer biology and developing tailored treatments to improve patient outcomes. Therefore, our results suggest that targeted therapy of these signaling pathways may be a promising approach in cancer therapy.

5. Conclusion

This study focuses on the vital role of critical proteins in the RAS signaling pathway in cancer development and progression. Notable proteins such as PDGFRB, PDGFB, IGF1, HRAS, HGF, FGF10, and ABL1 were identified, demonstrating their pivotal roles in various cellular processes and their implication in different cancer types. Oncogenes, including HRAS and BCR-ABL1, were found to be central in promoting uncontrolled cell proliferation, contributing to cancer initiation and maintenance. The study also highlighted NF1 as a critical tumor suppressor gene, essential for regulating cellular proliferation, with mutations leading to neurofibromatosis type 1. While actual experimental data is not provided here, it is crucial to note that the identification of these proteins has been supported by extensive literature and previous research in the field. For example, experimental studies have elucidated the specific roles of these proteins in cancer biology and demonstrated their dysregulation in various cancer types.

Additionally, targeted therapies such as Imatinib, Sunitinib, Crizotinib, Dasatinib, Nilotinib, Erdafitinib, and Balversa have shown promise in inhibiting the activity of some of these proteins in specific cancers, as evidenced by clinical trials and preclinical-studies. Understanding the complex roles of these proteins in cancer biology and their dysregulation provides essential insights into developing effective therapeutic strategies for improved patient outcomes. Our results suggest that targeting the signaling pathways involving these proteins holds significant promise as a valuable approach in cancer therapy. While not detailing specific experiments in this summary, the conclusions drawn are supported by a wealth of experimental evidence in the scientific literature, forming a robust foundation for further investigations and advancements in cancer treatment.

Author Contributions

The author did all the research work of this study.

Competing Interests

The author has declared that no competing interests exist.

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