REVIEW

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Exploring the promise of regulator of G Protein Signaling 20: insights into potential mechanisms and prospects across solid cancers and hematological malignancies

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Abstract

RGS (Regulator of G protein signaling) proteins have long captured the fascination of researchers due to their intricate involvement across a wide array of signaling pathways within cellular systems. Their diverse and nuanced functions have positioned them as continual subjects of scientific inquiry, especially given the implications of certain family members in various cancer types. Of particular note in this context is RGS20, whose clinical relevance and molecular significance in hepatocellular carcinoma we have recently investigated. These investigations have prompted questions into the prevalence of pathogenic mutations within the RGS20 gene and the intricate network of interacting proteins that could contribute to the complex landscape of cancer biology. In our study, we aim to unravel the mutations within the RGS20 gene and the multifaceted interplay between RGS20 and other proteins within the context of cancer. Expanding on this line of inquiry, our research is dedicated to uncovering the intricate mechanisms of RGS20 in various cancers. In particular, we have redirected our attention to examining the role of RGS20 within hematological malignances, with a specific focus on multiple myeloma and follicular lymphoma. These hematological cancers hold significant promise for further investigation, as understanding the involvement of RGS20 in their pathogenesis could unveil novel therapeutic strategies and treatment avenues. Furthermore, our exploration has extended to encompass the latest discoveries concerning the potential involvement of RGS20 in diseases affecting the central nervous system, thereby broadening the scope of its implications beyond oncology to encompass neurobiology and related fields.

Keywords RGS20, Mutation, Cancer, Hematological malignances, Epigenetic

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Background

Numerous biomarkers for cancer have subsequently been discussed [1–4], and potential targeted therapies focusing on important cancer associated genes have also long been on the rise [5–13]. In this list, RGS (Regulator of G protein signaling) proteins have recently attracted interest, especially RGS20. A number of studies have identified RGS20 in cancers such as oral squamous cell carcinoma [14], bladder cancer [15], kidney cancer [16], breast cancer [17], penile cancer [18], lung cancer [17, 19] and so on. Considering this, two primary concerns have emerged: firstly, the genetic and molecular relevance of RGS20 in cancer and its associated pathways warrants thorough examination. Secondly, it is crucial to understand how RGS20 is predominantly implicated in a wide array of solid cancers and hematological cancer types. The upcoming sections aim to address these concerns by providing a comprehensive summary and conducting an in-depth exploration of RGS20's involvement in cancer. Through these, we will shed light on potential mechanisms underlying RGS20's role in cancer initiation and progression, while also evaluating its potential as a diagnostic marker for various cancer types.

Potentially pathogenic mutations in RGS20

Mutations shape protein structure and function, impacting both normal physiology and the development of diseases like cancer [20, 21], which are key drivers of genetic diversity, introducing variations in the DNA sequence that can result in changes to the corresponding protein [22]. A single nucleotide mutation can alter amino acids, insertions, or deletions, significantly affecting the protein's structure and function [23]. This structural change can impact how the protein interacts with other molecules, thereby affecting its function in cellular processes. Mutation in protein structure and function plays a dual role: driving genetic diversity in evolution and contributing to disease development [24]. A deep understanding of these molecular processes is pivotal for advancing both foundational biological research and the creation of targeted therapies for genetic disorders and cancers.

The RGS20 gene was queried across 76,639 samples from 75,661 patients in 10 pan-cancer studies available on cBioPortal (https://www.cbioportal.org/). Overall, twenty mutations have been identified in RGS20. Among these, six mutations (A352V, E309Q, L359M, F284L, E309D, and S382L) were predicated as potential pathogenic mutations. Specifically, three mutations (A352V, E309Q, and L359M) were predicted to be pathogenic by three software tools—SIFT, Polyphen-2, and Mutation Assessor. These mutations are located in the highly conserved RGS domain of RGS20 (Fig. 1A). Additionally, three mutations (F284L, E309D, and S382L) were predicated as pathogenic by two software tools and are

also situated in highly conserved regions (Fig. 1A). The presence of these pathogenic mutations in the highly conserved region of the RGS20 gene may lead to severe pathological conditions. Pathogenic mutations play a critical role in driving the uncontrolled growth and survival of cells, thereby contributing significantly to the development and progression of cancer [20]. These mutations may disrupt key cellular processes, leading to the loss of normal regulatory mechanisms and the initiation of oncogenic transformation. Several pathogenic mutations in various cancers have been shown to exacerbate the disease. However, to date, there have been no studies reporting on the role of these mutations in cancer progression, necessitating further research.

SIFT (Sorting Intolerant From Tolerant) is an in silico tool used to analyze amino acid substitutions in protein sequences. It categorizes substitutions as either "tolerated" (unlikely to affect protein function) or "not tolerated" (potentially impacting protein function), considering amino acid features and homology to make predictions. PolyPhen-2 (Polymorphism Phenotyping v2) is another predictive tool that assesses the impact of amino acid substitutions on protein function using a structure-based approach. Its performance is comparable to tools like Mutation Assessor, SIFT, and Condel. Mutation Assessor predicts the functional impact of amino acid substitutions, focusing on mutations found in cancer or missense polymorphisms. It evaluates the evolutionary conservation of affected amino acids across protein homologs to make assessments.

Structural and functional sites in RGS20 protein
Protein-protein interactome of RGS20

Protein-protein interactions (PPIs) play a fundamental role in coordinating cellular processes, regulating diverse biological functions. This intricate network of interactions is essential for signal transduction, enzymatic activity, structural support, and numerous other cellular activities [25]. The dysregulation of PPIs has been linked to various diseases, underscoring the importance of comprehending these interactions for advancing both basic biological understanding and therapeutic development [26–28]. Aberrant PPIs have been implicated in the pathogenesis of various diseases, such as cancer and neurodegenerative disorders [27]. In cancer, for instance, disrupted interactions among oncogenic proteins or the absence of interactions involving tumor suppressors can lead to unchecked cell proliferation and the development of malignancy [29].

RGS20 interacts directly or indirectly with variety of molecules including FAF2, BOLA1, TXLNA, TTC7B, ARHGAP26, RGS14, RGS16, RGS17, RGS18, RGS19, RGS21, GNAI1, GNAI2, GNAI3, GNAT, STMN2, GNAO1, MTNR1B, GNAZ, and CATSPER1 (Fig. 1B
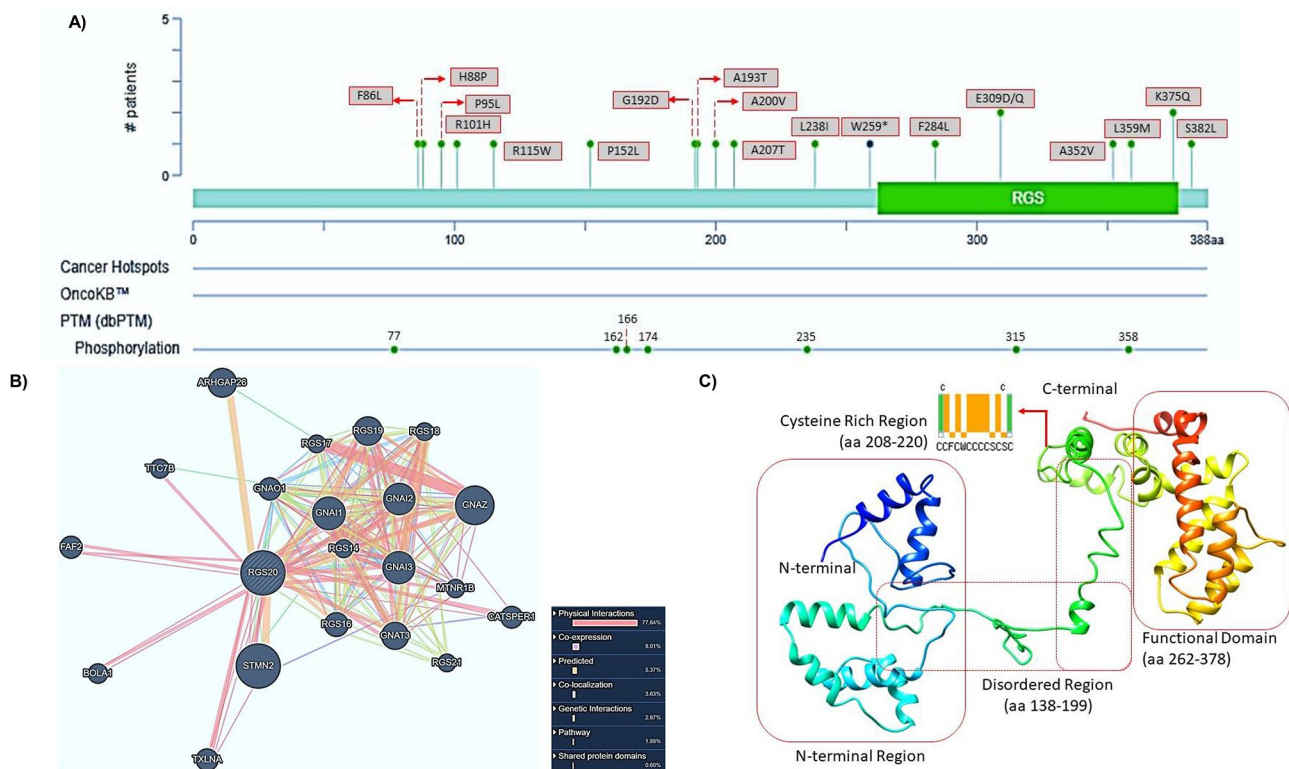
Fig. 1 **A**) Potential pathogenic mutations for RGS20. **B**) Protein-protein interactions between RGS20 with other proteins. **C**) The three-dimensional structure of RGS20, featuring its functional domain and cysteine-rich region

and supplementary Table 1). Molecules such as RGS14, RGS16, RGS17, RGS18, RGS19, and RGS21 are involved in regulating the G-protein coupled receptor signaling cascade. GNAI1, GNAI2, and GNAI3 serve as modulators or transducers in various transmembrane signaling pathways. Other molecules are implicated in diverse functions such as endoplasmic reticulum-associated degradation and regulation of phosphatidylinositol 4-phosphate. It is well-established that RGS20, similar to other members of the Regulators of G protein Signaling (RGS) family, functions as a GTPase-activating protein (GAP) for the alpha subunits of heterotrimeric G proteins. Specifically, RGS proteins enhance the hydrolysis of GTP to GDP by Gα subunits, thereby facilitating the termination of G protein-mediated signaling. GNAI1, GNAI2, and GNAI3, belonging to the Gαi subfamily, participate in inhibitory signaling pathways. RGS proteins, including RGS20, play a critical role in modulating the duration and strength of G protein signaling by accelerating the intrinsic GTPase activity of Gαsubunits. However, detailed information regarding the specific molecular functions of RGS20 in its interactions with FAF2, BOLA1, TXLNA, TTC7B, ARHGAP26, RGS14, RGS16, RGS17, RGS18, RGS19, RGS21, GNAI1, GNAI2, GNAI3, MTNR1B, GNAZ, and CATSPER1 is currently not extensively documented in the literature.

RGS20 structure with its domain and motifs

The importance of protein structure in disease cannot be overstated, as the three-dimensional arrangement of proteins profoundly influences their functions [30–32]. Any disturbance to this structure can result in pathological conditions [32]. Proteins participate in numerous biological processes, including enzymatic reactions, signal transmission, and providing structural support. Diseases often originate from mutations or events that lead to the misfolding of crucial proteins, disrupting their intended functions [33]. Changes in enzyme structure may interfere with essential metabolic pathways, while misfolded signaling proteins can disrupt normal cellular communication [34, 35]. Moreover, protein misfolding is a defining characteristic of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, where aggregates of misfolded proteins contribute to dysfunction in neurons [34, 36, 37]. Understanding the connection between protein structure and disease is essential for developing targeted therapeutic approaches aimed at correcting or mitigating these structural defects, thereby restoring normal cellular function.

The structural analysis of RGS20 reveals a functional domain located at the C-terminal region spanning amino acids 262 to 378 (see Fig. 1C). Within this region, a total of seven mutations have been identified, with five mutations—A352V, E309Q, L359M, F284L, and E309D—being

identified as potentially pathogenic. Mutations occurring within functional domains of proteins can have significant adverse effects on cellular processes and are implicated in various diseases. These mutations have the potential to disrupt the precise structure and function of critical protein domains, resulting in either loss-of-function or gain-of-function effects. For instance, mutations in the kinase domain of the epidermal growth factor receptor (EGFR) are known to contribute to uncontrolled cell proliferation in certain cancers [38]. Similarly, mutations in the DNA-binding domain of the tumor suppressor p53 disrupt its ability to regulate cell cycle progression and apoptosis, thereby contributing to cancer development [39]. Maintaining the integrity of functional domains is crucial, as mutations that disrupt these domains can significantly impair cellular function and contribute to the development of cancers.

RGS20 also contains a cysteine-rich domain spanning from amino acid 208 to amino acid 220 (Fig. 1C). Cysteine-rich domains are pivotal in diverse biological processes, contributing to the structural integrity and functional versatility of proteins [40]. Cysteine, with its unique thiol group, plays a crucial role in forming disulfide bonds that confer stability and maintain the three-dimensional structure of proteins. Proteins containing cysteine-rich domains frequently engage in redox reactions, detecting changes in the cellular environment and transmitting signals accordingly [41]. Moreover, cysteine-rich domains are common in metal-binding proteins, where cysteine residues coordinate with metal ions, thereby influencing both catalytic activity and structural

stability [42]. Examples encompass zinc finger domains crucial for transcriptional regulation and the metallothionein family, pivotal in maintaining metal homeostasis. Cysteine-rich domains in proteins contribute significantly to their overall functionality, enabling interactions with other molecules, involvement in signal transduction pathways, and serving as pivotal components in diverse physiological and pathological processes [43].

RGS20 implicated in cancers

The mutation of RGS20 and its interaction with other proteins can lead to genetic and epigenetic alterations, potentially contributing to the onset and progression of various diseases, particularly cancer. Therefore, it is plausible to suggest that RGS20 may exert influence on the development and advancement of cancer. As a proof, we conducted a comprehensive analysis of RGS20 gene expression across a wide range of cancer types, including ACC, BLCA, BRCA, CESC, CHOL, COAD, DLBC, ESCA, GBM, HNSC, KICH, KIRC, KIRP, LAML, LGG, LIHC, LUAD, LUSC, MESO, OV, PAAD, PCPG, PRAD, READ, SARC, SKCM, STAD, TGCT, THCA, THYM, UCEC, UCS, and UVM, using Timer 2 (https://timer.cistrome.org/) tool as shown in Fig. 2A. This tool facilitates the dynamic generation of high-quality figures for comprehensive exploration of tumor immunological, clinical, and genomic features [44]. The Gene_DE module within this tool is utilized to analyze the differential expression of any gene of interest between tumor and adjacent normal tissues across all TCGA (The Cancer Genome Atlas) cancers. Our analysis revealed that in 21 of the cancer
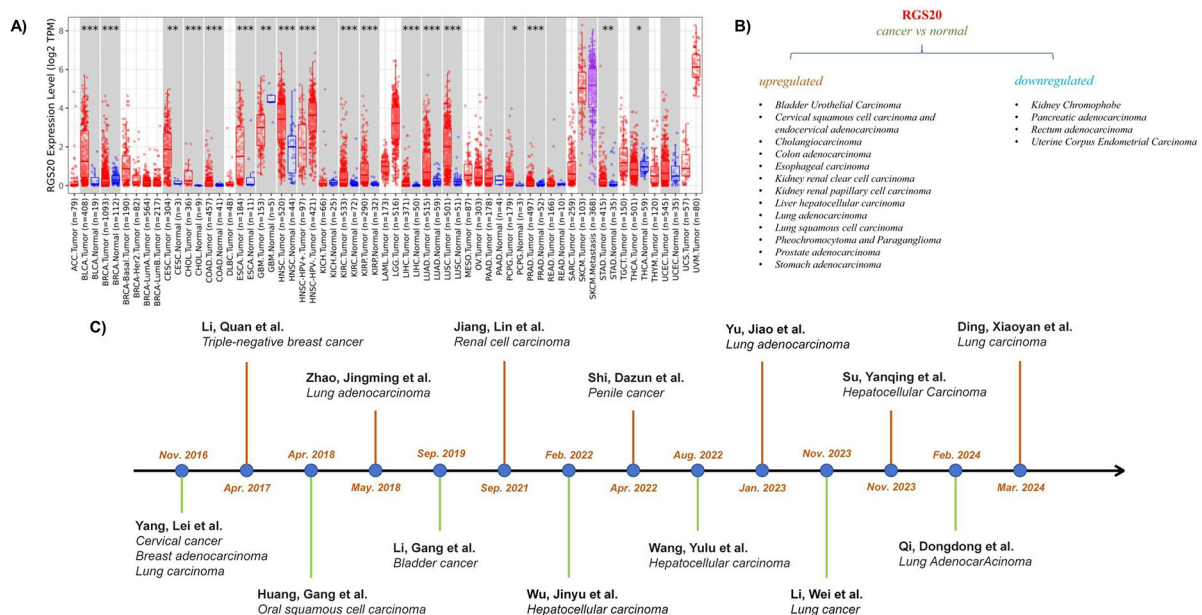

Fig. 2 **A**) Expression of RGS20 in diverse cancers and associated normal samples. **B**) Gene expression patterns of upregulated and downregulated RGS20 in various cancers. **C**) Timeline of RGS20 involvement in different cancer types

types examined, for which both normal and tumor samples were available, RGS20 gene expression showed distinct patterns. Specifically, we observed upregulation of RGS20 in most cancers, including BLCA, CESC, CHOL, COAD, ESCA, KIRC, KIRP, LIHC, LUAD, LUSC, PCPG, PRAD, and STAD, compared to their respective normal samples (Fig. 2B). On the other hand, RGS20 was found to be downregulated in several tumor types, such as BRCA, GBM, HNSC, and THCA (Fig. 2B). Notably, we observed no significant change in RGS20 expression in KICH, PAAD, READ, and UCEC. These findings provide valuable insights into the diverse expression patterns of RGS20 across different cancer types, suggesting its potential involvement in the development and progression of these cancers. Furthermore, an increasing number of publications have provided further support for RGS20's involvement in various types of cancer. As illustrated in Fig. 2C, a growing body of literature underscores the importance of RGS20 across different types of cancer. To further explore its role in cancer, our focus on uncovering the underlying mechanisms through which RGS20 exerts its effects.

The putative mechanism of RGS20 in cancers: tumor related pathways and epigenetics

Understanding the mechanisms by which RGS20 operates in cancer will not only enhance our comprehension of its role in the disease but also offer valuable insights for identifying potential therapeutic targets for cancer patients. As illustrated in Figs. 3 and 4, we have compiled

the potential mechanisms through which RGS20 influences cancers.

A recent study has revealed that RGS20 has the capability to activate NF-κB signaling, which plays a pivotal role in mediating RGS20's impact on the proliferation, migration, and tumorigenicity of bladder cancer cells [15]. Moreover, RGS20 might accelerate penile cancer progression by regulating PI3K/AKT signaling activation [18]. Similarly, in liver cancer, RGS20's oncogenic role seems to be linked to the PI3K/AKT/mTOR signaling pathway [45]. The promotion of non-small cell lung carcinoma proliferation by RGS20 is attributed to its induction of autophagy and inhibition of the PKA-Hippo signaling pathway [19]. NF-κB signaling has been implicated in the progression and treatment of various cancers [46–50], and its activation is associated with all recognized cancer hallmarks [46]. Furthermore, PI3K/AKT signaling holds significance in cancer contexts [51–53]. Additionally, PKA/Hippo signaling is crucial for cancer, as it has been shown to affect cancer stem cells [54]. Hence, these three tumor-related signaling pathways likely contribute to the oncogenic effects of RGS20 in cancers.

In addition to genetic alterations, the role of epigenetics is increasingly recognized as pivotal in cancer development [55–57]. Investigating epigenetics in cancer offers valuable insights into disease mechanisms. Epigenetics encompasses heritable traits that are independent of DNA sequence and involves three primary forms of regulation: DNA methylation, histone modification, and noncoding RNA activity [58]. The NEAT1/miR-365/
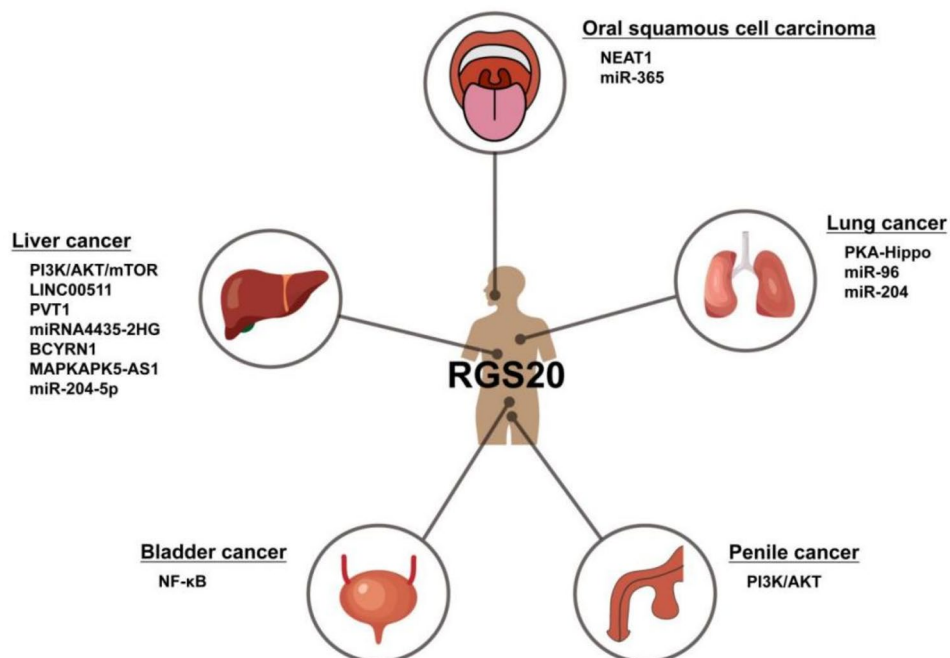

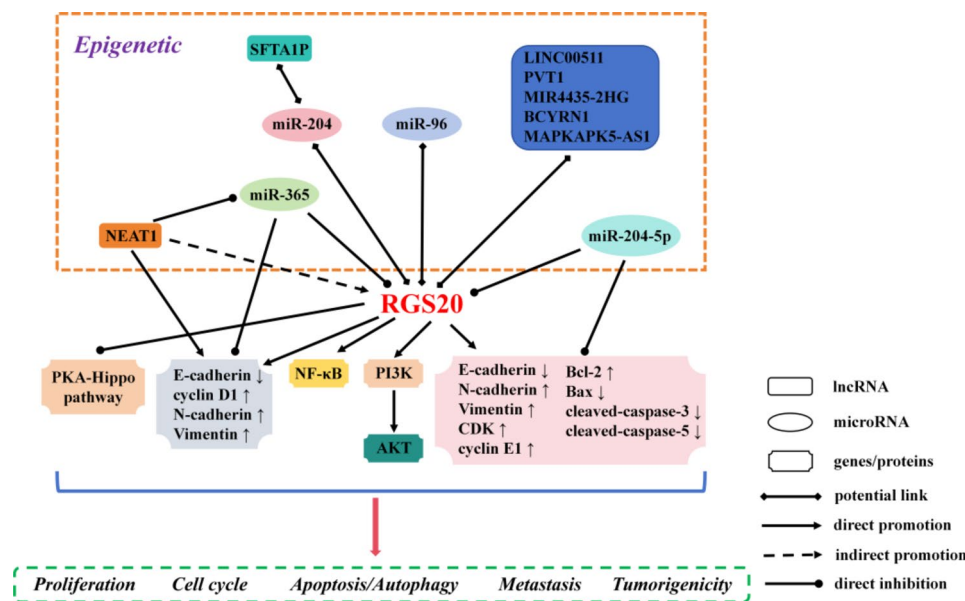**Fig. 3** An overview of the impact of RGS20 across various cancer types

Fig. 4 Visualization outlining the relevant signaling pathways and epigenetic factors of RGS20 in cancer contexts

RGS20 axis has been identified as influential in cell proliferation and invasion in oral squamous cell carcinoma (OSCC) by modulating the expression of key markers like E-cadherin, cyclin D1, N-cadherin, and Vimentin [14]. Notably, NEAT1 and miR-365 are implicated in OSCC [59–63]. In lung adenocarcinoma, RGS20 expression is regulated by hsa-miR-204, controlled by the long noncoding RNA (lncRNA) SFTAIP, and targeted by hsa-miR-96 [64]. RGS20 is also linked with several lncRNAs (LINC00511, PVT1, MIR4435-2HG, BCYRN1, and MAPKAPK5-AS1) in hepatocellular carcinoma [45], with these lncRNAs already known to be involved in HCC [65–69]. Moreover, microRNA-204-5p exerts inhibitory effects on HCC proliferation, apoptosis, and migration/invasion by targeting RGS20 [13], underscoring the intricate regulatory network involving RGS20 and noncoding RNAs in cancer. Furthermore, palmitoylation serves as a regulatory mechanism controlling RGS20 function, inhibiting Gαo signaling through cAMP signaling rather than GAP (GTPase accelerating protein) activity [70], thereby broadening the potential mechanisms through which RGS20 may impact cancer. In summary, the interplay between RGS20, epigenetics, and cancer, particularly involving noncoding RNAs, suggests a significant role for epigenetic regulation in RGS20-mediated oncogenesis.

The role of RGS20 as a prognostic factor for cancer patients

Prognostic factors play a crucial role in categorizing newly diagnosed cancer patients into high or low-risk groups, influencing treatment decisions and predicting outcomes [71–73]. Many of these prognostic factors, including specific genes/proteins, have also been identified as potential therapeutic targets across various cancers [74–78], underscoring the importance of furthering our understanding of these factors in cancer patients.

As RGS20 plays a role in modifying the genetic and epigenetic landscape of cancer, it holds promise as a potential prognostic indicator for various malignancies. To substantiate this claim, we have gathered relevant publications focusing on RGS20 as a prognostic factor, as detailed below. RGS20 demonstrated elevated expression in tumor samples compared to normal samples, and it was associated with poor prognosis in lung adenocarcinoma [19, 64, 79]. The study further highlighted the application of RGS20 in subgroup analysis based on clinical features such as age, gender, and stage, further revealing a correlation between high RGS20 expression and lower survival rates in lung adenocarcinoma [64]. RGS20 expression is upregulated in bladder cancer compared to control, both in clinical patients samples and cell lines, and high RGS20 expression is associated with worse 5-year overall survival [15]. A study combining WGCNA results from GEO datasets and experimental data from analyzing the sera of 10 HCC cases and 10 NCs via human proteomics chip, identified RGS20 as one of the 11 TAAs (tumor-associated antigens) candidates for hepatocellular carcinoma (HCC) [80], indicating the potential prognostic ability of RGS20 for HCC patients. Furthermore, a recent study revealed that RGS20 exhibited high expression in HCC compared to normal adjacent tissues and suggested its potential prognostic value for HCC [45]. RGS20 expression was found to be increased in renal cell carcinoma (RCC) samples and cell lines compared to relative controls, and its upregulation is associated with poor prognosis for RCC patients [16].

Table 1 The prognostic significance of RGS20 in a variety of cancer types

Cancer types	Prognostic
Lung adenocarcinoma	Poor
Bladder cancer	Poor
Hepatocellular carcinoma	Poor
Renal cell carcinoma	Poor
Triple-negative breast cancer	Poor
Penile cancer	Poor

Table 2 RGS20 significantly impacts the development and progression of various cancers

Cancer types		Potential mechanisms
Oral squamous cell carcinoma	proliferation, invasion and cell cycle	NEAT1/miR-365/RGS20 axis
Bladder cancer	proliferation, migration and tumorigenicity	NF-κB signaling
Renal cell carcinoma	proliferation, migration, invasion, cell cycle and apoptosis	-
Penile cancer cells	proliferation, migration, invasion and tumor growth	PI3K/AKT signaling
Cervical cancer	metastasis	-
Breast adenocarcinoma	metastasis	-
Lung carcinoma	metastasis, proliferation, autophagy	PKA/Hippo signaling, hsa-miR-96 and hsa-miR-204
Hepatocellular carcinoma	proliferation, apoptosis, migration and invasion	PI3K/Akt/mTOR signaling, LINC00511, PVT1, MIR4435-2HG, BCYRN1, MAPKAPK5-AS1 and miRNA-204-5p

A study focusing on breast cancer found that RGS20 expression decreased in luminal breast cancer tissues, was upregulated in triple-negative breast cancer (TNBC) tissues, and showed no alteration in HER2-positive breast cancer tissues compared to normal tissues, with high RGS20 expression being associated with a poor prognosis in TNBC patients [81]. In penile cancer, a relatively uncommon cancer, the prognostic role of RGS20 has also been observed, with high expression levels in tumor samples compared to normal samples and a correlation with unfavorable clinical outcomes [18].

In summary, numerous studies provide accumulating evidence supporting the prognostic significance of RGS20 across a spectrum of cancers, including lung adenocarcinoma, bladder cancer, hepatocellular carcinoma, renal cell carcinoma, triple-negative breast cancer, and penile cancer (as summarized in Table 1). These studies consistently report elevated levels of RGS20 expression in tumor tissues and cell lines compared to normal counterparts. Furthermore, high RGS20 expression consistently correlates with poor prognosis in these cancer types, suggesting its potential role as an oncogene. These findings underscore the importance of RGS20 as a potential biomarker for predicting disease prognosis and highlight its potential as a therapeutic target for intervention in various cancers.

RGS20 plays a pivotal role in influencing the growth, survival, and metastasis of cancers

Various cellular processes can be targeted to impede the growth of cancer cells. Considering RGS20 as a potential prognostic candidate for cancers, we outline its impact on cancer cells. RGS20 has been demonstrated to hasten the proliferation and invasion of oral squamous cell carcinoma (OSCC) cell lines, affecting cell cycle progression [14]. In bladder cancer, RGS20 overexpression fosters cell proliferation and migration in vitro, while also augmenting tumorigenicity in vivo [15]. Knockdown of RGS20 in renal cell carcinoma (RCC) cells results in diminished proliferation, migration, and invasion, coupled with cell cycle arrest and increased apoptosis [16]. Modifying RGS20 expression in penile cancer cells through knockdown and overexpression techniques impacts their proliferation, migration, and invasion

abilities, with specific targeting of RGS20 through knockdown leading to decreased tumor growth in vivo [18]. Furthermore, studies indicate that manipulating RGS20 expression in cervical cancer, breast adenocarcinoma, and non-small cell lung carcinoma cells influences cell mobility and adhesive properties, suggesting a potential role in promoting metastasis [17]. RGS20 enhances the proliferation of non-small cell lung carcinoma by activating autophagy [19]. Targeting RGS20 has been implicated in the regulation of critical cellular processes, including cell proliferation, apoptosis, migration, and invasion in HCC [13]. Taken together, these findings underscore the multifaceted role of RGS20 in governing key cellular processes and support its oncogenic role in cancer as shown in Table 2.

RGS20 holds promise for potential involvement in hematological malignancies

Numerous studies have documented the involvement of various RGS proteins in several hematological malignancies, including myeloma [82], leukemia [83, 84], and lymphoma [85]. Therefore, the RGS protein family plays a critical role in hematological malignancies. Given the potential involvement of RGS20 in various cancers and the limited information on its role in hematological malignancies, investigating RGS20 in this context is crucial. To address this, we conducted a bioinformatic analysis to predict its potential role in different hematological malignancies, including AML (acute myeloid leukemia), ALL (acute lymphoblastic leukaemia), CLL (chronic lymphocytic leukemia), DLBCL (diffuse large B cell lymphoma), BL (burkitt lymphoma), FL (follicular

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lymphoma), T-lymphoma, and MM (multiple myeloma). We utilized datasets such as GSE4475 (burkitt lymphoma), GSE16131 (follicular lymphoma), GSE22762 (chronic lymphocytic leukemia), GSE24080 (multiple myeloma), GSE28703 (acute lymphoblastic leukemia), GSE31312 (diffuse large B-cell lymphoma), GSE37642 (acute myeloid leukemia), and GSE58445 (T-cell lymphoma), obtained from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). Data processing followed previously described methods [86]. Additionally, functional gene enrichment pathways were derived from the Kyoto Encyclopedia of Genes and Genomes (KEGG) process, selected based on their significant P values ($P < 0.05$). Given RGS20's prognostic capabilities in cancer and its influence on cancer via the NF-κB, PI3K/AKT and PKA/Hippo pathways, we employed KEGG pathway analysis (top 10 enriched pathways) to assess RGS20-correlated pathways in hematological malignancies. Our analysis revealed a correlation between RGS20 and the PI3K/AKT pathway in multiple myeloma (MM) and follicular lymphoma (FL). However, we found no direct association of RGS20 with the PKA/Hippo or NF-κB pathways in hematological malignancy, as shown in supplementary Fig. 1. The PI3K/AKT signaling pathway has been documented to potentially activate in follicular lymphoma [87], and suppressing this pathway has been demonstrated to modify the immune microenvironment of follicular lymphoma [88]. Furthermore, the PI3K/AKT signaling pathway has been identified as a pivotal signaling cascade in myeloma [89, 90].

AKT protein, a key component of the PI3K/AKT pathway, has been demonstrated to be significant in multiple myeloma (MM) [91–94] and follicular lymphoma (FL) [87, 95]. We applied molecular docking analysis to evaluated the potential interaction of RGS20 protein with AKT proteins (AKT1, AKT2 and AKT3). We utilized ZDOCK 3.0.21 to predict the binding modes of RGS20 with AKT1-3 proteins, respectively. Prior to docking, we obtained the structural files of AKT3 and RGS20 proteins from the AlphaFold database, while the crystal structures of AKT1 and AKT2 were downloaded from the PDB database with PDB IDs 7NH5 for AKT1 and 8Q61 for AKT2. Subsequently, we processed them using PyMol 2.5.32, including the removal of inaccurately predicted structural regions. For docking, we employed the default settings of ZDOCK 3.0.2 and performed global rigid docking. Following docking, energy minimization was

conducted using AMBER18 under the ff14SB force field. Finally, the conformation of the protein complexes after energy minimization was evaluated for binding affinity using the online tool prodigy3 (https://wenmr.science.uu.nl/prodigy/) and visualized using PyMOL 2.5.3 for further analysis.

Table 3 illustrates the binding affinity of protein-protein complexes based on docking scores. Negative values indicate potential binding capability, with smaller values indicating stronger binding. Notably, the binding energies for RGS20-AKT1, RGS20-AKT2, and RGS20-AKT3 were −10.5, -8.9, and −15.2 kcal/mol, respectively, indicating favorable binding effects. Further analysis of their binding modes and forces was conducted, as depicted in Fig. 5B-C. During the formation of the AKT1-RGS20 complex, hydrogen bonds and salt bridges were observed between specific residues on both proteins. Similar interactions were observed in the AKT2-RGS20 and AKT3-RGS20 complexes. These interactions constitute the main mode of interaction between AKT proteins and RGS20, indicating strong binding affinity in all complexes. These results strengthen the potential association between RGS20 and the PI3K/AKT pathway. Indeed, it's imperative to recognize that other pivotal proteins within the PI3K/AKT pathway may also establish significant connections with the RGS20 protein. These interactions warrant attention and should not be overlooked. Further analysis or experiments are necessary to substantiate these connections.

RGS20 implicated in brain disorders

Besides RGS20 in cancers, recently the increasing evidence showed that RGS20 might be involved in brain correlated diseases. A study focused on sporadic early-onset Alzheimer's disease (EOAD), autosomal dominant Alzheimer's disease (ADAD), sporadic frontotemporal dementia (sFTD) and genetic frontotemporal dementia (gFTD) were published recently which six common differentially expressed genes (DEG) for all the patients' groups compared with controls: RGS20, WIF1, HSPB1, EMP3, S100A11 and GFAP [96]. In addition, seven SNPs in SNX31, RORA, CDH23, RGS20, LRRC4C, MAPK6PS1, LOC105378355 were found potential associated with CSF BACE activity, a potential diagnostic biomarker for Alzheimer disease [97]. Furthermore, RGS20 is a novel potential target for the treatment of depression [98, 99]. Thus, the role of RGS20 in brain diseases cannot be overlooked. Since a study demonstrated the crosstalk across cancer and neurodegeneration [100], it is reasonable to highlight the RGS20 in brain diseases (See Fig. 6) even it looks a potential candidate for cancers. However, the current investigations lack the potential mechanism of RGS20 in brain disease. So further explorations

Table 3 The binding affinity of the RGS20 protein with AKT proteins

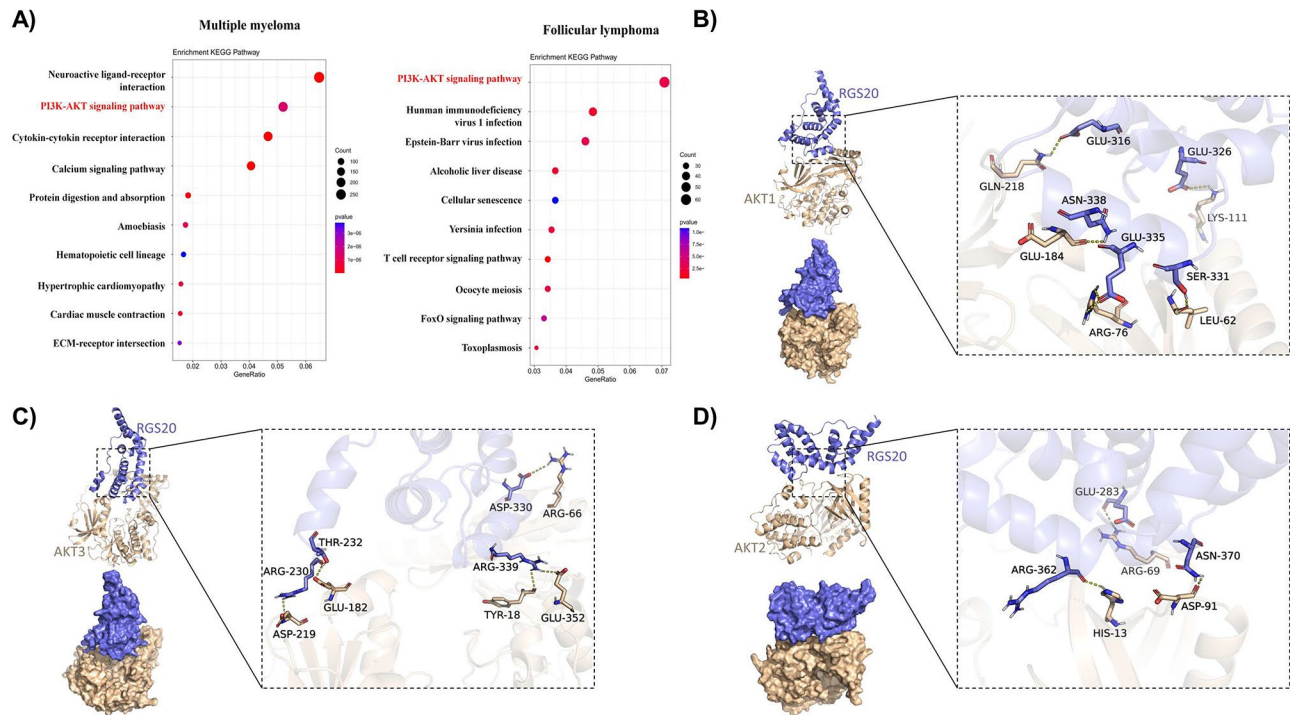| Complex	Predicted binding affinity (kcal/mol)
RGS20-AKT1	-10.5
RGS20-AKT2	-8.9
RGS20-AKT3	-15.2

Fig. 5 (**A**) KEGG analysis on multiple myeloma and follicular lymphoma. The binding modes and binding forces between RGS20 protein and AKTs proteins: RGS20-AKT1 (**B**), RGS20-AKT3 (**C**) and RGS20-AKT2 (**D**)
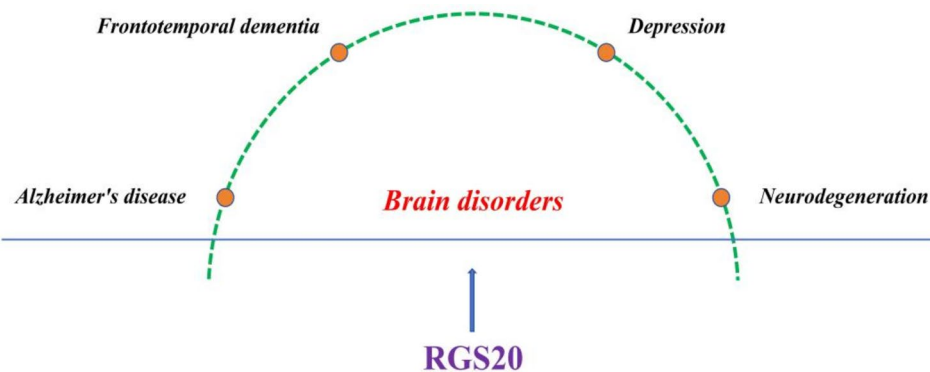

Fig. 6 RGS20 is implicated in various brain disorders, including Alzheimer's disease, frontotemporal dementia, depression, and neurodegeneration

are needed to demonstrate its potential mechanism of RGS20 in brain diseases.

Conclusion

In this study, we've discerned potential mutations in RGS20 and its interactions with other proteins, suggesting disturbances in typical molecular pathways. These altered molecular processes in cancer cells may contribute to their development and proliferation. Furthermore, both epigenetic and genetic mechanisms have been implicated in RGS20's role in fostering the growth and metastasis of cancer cells. There is accumulating evidence indicating that RGS20 possesses prognostic capabilities across a spectrum of cancers and may function as a potential oncogene. Particularly noteworthy is its impact on hematological malignancies, such as multiple myeloma (MM) and follicular lymphoma (FL), indicating promising avenues for further investigation. Nonetheless, additional research is imperative to elucidate the specific roles of RGS20 in various subtypes of hematological malignancies. Furthermore, the exploration of RGS20's involvement in brain diseases presents a compelling opportunity for further inquiry, potentially yielding valuable insights into its broader physiological significance. Our study significantly contributes to the burgeoning body of evidence supporting RGS20 as a potential molecular biomarker for prognostic stratification and as a novel therapeutic target across diverse disease contexts.

Continued research efforts in this domain hold the potential to deepen our understanding of RGS20's multifaceted roles in disease pathogenesis and inform the development of targeted interventions.

Abbreviations

LAML   Acute Myeloid Leukemia
ACC   Adrenocortical carcinoma
BLCA   Bladder Urothelial Carcinoma
LGG   Brain Lower Grade Glioma
BRCA   Breast invasive carcinoma
CESC   Cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL   Cholangiocarcinoma
LCML   Chronic Myelogenous Leukemia
COAD   Colon adenocarcinoma
CNTL   Controls
ESCA   Esophageal carcinoma
FPPP   FFPE Pilot Phase II
GBM   Glioblastoma multiforme
HNSC   Head and Neck squamous cell carcinoma
KICH   Kidney Chromophobe
KIRC   Kidney renal clear cell carcinoma
KIRP   Kidney renal papillary cell carcinoma
LIHC   Liver hepatocellular carcinoma
LUAD   Lung adenocarcinoma
LUSC   Lung squamous cell carcinoma
DLBC   Lymphoid Neoplasm Diffuse Large B-cell Lymphoma
MESO   Mesothelioma
MISC   Miscellaneous
OV   Ovarian serous cystadenocarcinoma
PAAD   Pancreatic adenocarcinoma
PCPG   Pheochromocytoma and Paraganglioma
PRAD   Prostate adenocarcinoma
READ   Rectum adenocarcinoma
SARC   Sarcoma
SKCM   Skin Cutaneous Melanoma
STAD   Stomach adenocarcinoma
TGCT   Testicular Germ Cell Tumors
THYM   Thymoma
THCA   Thyroid carcinoma
UCS   Uterine Carcinosarcoma
UCEC   Uterine Corpus Endometrial Carcinoma
UVM   Uveal Melanoma

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Author contributions

Conceptualization, Y.W. and F.L.; data analysis, Y.W., J.Q., T.C.D and R.B.; writing—original draft preparation, Y.W. and A.S.; writing—review and editing, all co-authors; supervision, F.L.; project administration, F.L. All authors have read and agreed to the published version of the manuscript.

Data availability

 The datasets analyzed during the current study are downloaded in the GEO repository, https://www.ncbi.nlm.nih.gov/geo/.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

References

1.   Sarhadi VK, Armengol G. Mol Biomarkers Cancer Biomolecules, 2022. 12(8).
2.   Xu Y, et al. Identification of BANF1 as a novel prognostic biomarker in gastric cancer and validation via in-vitro and in-vivo experiments. Aging. 2024;16(2):1808–28.
3.   Tintelnot J, et al. Microbiota-derived 3-IAA influences chemotherapy efficacy in pancreatic cancer. Nature. 2023;615(7950):168–74.
4.   Mishra A, Verma M. Cancer biomarkers: are we ready for the prime time? Cancers (Basel). 2010;2(1):190–208.
5.   Alcantara MB, et al. Targeting STAT3 in tumor-associated antigen-presenting cells as a strategy for kidney and bladder cancer immunotherapy. Front Immunol. 2023;14:1274781.
6.   Li GX et al. GRIN2A mutation is a novel indicator of stratifying beneficiaries of immune checkpoint inhibitors in multiple cancers. Cancer Gene Ther, 2024.
7.   Yu S, et al. LOXL1-AS1 inhibits JAK2 ubiquitination and promotes cholangiocarcinoma progression through JAK2/STAT3 signaling. Cancer Gene Ther; 2024.
8.   Im JY, et al. CYB5R3 functions as a tumor suppressor by inducing ER stress-mediated apoptosis in lung cancer cells via the PERK-ATF4 and IRE1alpha-JNK pathways. Exp Mol Med. 2024;56(1):235–49.
9.   Wang B, et al. Tumor-intrinsic RGS1 potentiates checkpoint blockade response via ATF3-IFNGR1 axis. Oncoimmunology. 2023;12(1):2279800.
10.   Lin Q et al. Long noncoding RNA HITT coordinates with RGS2 to inhibit PD-L1 translation in T cell immunity. J Clin Invest, 2023. 133(11).
11.   Li C, et al. The G protein signaling regulator RGS3 enhances the GTPase activity of KRAS. Science. 2021;374(6564):197–201.
12.   Huang D, et al. Targeting regulator of G protein signaling 1 in tumor-specific T cells enhances their trafficking to breast cancer. Nat Immunol. 2021;22(7):865–79.
13.   Su Y, et al. MicroRNA-204-5p inhibits Hepatocellular Carcinoma by Targeting the Regulator of G Protein Signaling 20. ACS Pharmacol Transl Sci. 2023;6(12):1817–28.
14.   Huang G, He X, Wei XL. lncRNA NEAT1 promotes cell proliferation and invasion by regulating miR–365/RGS20 in oral squamous cell carcinoma. Oncol Rep. 2018;39(4):1948–56.
15.   Li G, et al. Regulator of G protein signaling 20 promotes proliferation and migration in bladder cancer via NF-kappaB signaling. Biomed Pharmacother. 2019;117:109112.
16.   Jiang L, et al. Association of RGS20 expression with the progression and prognosis of renal cell carcinoma. Oncol Lett. 2021;22(3):643.
17.   Yang L, et al. Regulator of G protein signaling 20 enhances cancer cell aggregation, migration, invasion and adhesion. Cell Signal. 2016;28(11):1663–72.
18.   Shi D et al. *RGS20 Promotes Tumor Progression through Modulating PI3K/AKT Signaling Activation in Penile Cancer.* J Oncol, 2022. 2022: p. 1293622.
19.   Ding X, et al. RGS20 promotes non-small cell lung carcinoma proliferation via autophagy activation and inhibition of the PKA-Hippo signaling pathway. Cancer Cell Int. 2024;24(1):93.
20.   Torgovnick A, Schumacher B. DNA repair mechanisms in cancer development and therapy. Front Genet. 2015;6:157.
21.   Olivier M, Hollstein M, Hainaut P. TP53 mutations in human cancers: origins, consequences, and clinical use. Cold Spring Harb Perspect Biol. 2010;2(1):a001008.
22.   Loewe L, Hill WG. The population genetics of mutations: good, bad and indifferent. Philos Trans R Soc Lond B Biol Sci. 2010;365(1544):1153–67.
23.   Savino S, Desmet T, Franceus J. Insertions and deletions in protein evolution and engineering. Biotechnol Adv. 2022;60:108010.

24. Tenaillon O, Matic I. The impact of neutral mutations on genome evolvability. Curr Biol. 2020;30(10):R527–34.

25. Rao VS, et al. Protein-protein interaction detection: methods and analysis. Int J Proteom. 2014;2014:p147648.

26. Kenanova DN, et al. A systematic Approach to the Discovery of Protein-Protein Interaction stabilizers. ACS Cent Sci. 2023;9(5):937–46.

27. Olah J et al. Challenges in discovering drugs that target the protein-protein interactions of disordered proteins. Int J Mol Sci, 2022. 23(3).

28. Petta I, et al. Modulation of protein-protein interactions for the development of Novel therapeutics. Mol Ther. 2016;24(4):707–18.

29. Rodon J, Tabernero J. Improving the armamentarium of PI3K inhibitors with isoform-selective agents: a New Light in the darkness. Cancer Discov. 2017;7(7):666–9.

30. Dhakar R, Dakal TC, Sharma A. Genetic determinants of lung cancer: understanding the oncogenic potential of somatic missense mutations. Genomics. 2022;114(4):110401.

31. Mathur R, et al. Predicting the functional consequences of genetic variants in co-stimulatory ligand B7-1 using in-silico approaches. Hum Immunol. 2021;82(2):103–20.

32. Dakal TC, et al. Predicting the functional consequences of non-synonymous single nucleotide polymorphisms in IL8 gene. Sci Rep. 2017;7(1):6525.

33. Dakal TC, Kumar R, Ramotar D. Structural modeling of human organic cation transporters. Comput Biol Chem. 2017;68:153–63.

34. Sharma A, et al. Common genetic variants associated with Parkinson's disease display widespread signature of epigenetic plasticity. Sci Rep. 2019;9(1):18464.

35. Sharma A, et al. Epigenetic Regulatory Enzymes: mutation prevalence and coexistence in cancers. Cancer Invest. 2021;39(3):257–73.

36. Dworschak GC, et al. Biallelic and monoallelic variants in PLXNA1 are implicated in a novel neurodevelopmental disorder with variable cerebral and eye anomalies. Genet Med. 2021;23(9):1715–25.

37. Deepika, et al. Naringenin orchestrates and regulates the reactive oxygen species-mediated pathways and Proinflammatory Signaling: Targeting Hallmarks of Aging-Associated disorders. Rejuvenation Res. 2024;27(1):3–16.

38. Lynch TJ, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350(21):2129–39.

39. Soussi T, Wiman KG. TP53: an oncogene in disguise. Cell Death Differ. 2015;22(8):1239–49.

40. Berg JM, Shi Y. The galvanization of biology: a growing appreciation for the roles of zinc. Science. 1996;271(5252):1081–5.

41. Maret W. Zinc biochemistry: from a single zinc enzyme to a key element of life. Adv Nutr. 2013;4(1):82–91.

42. Laity JH, Lee BM, Wright PE. Zinc finger proteins: new insights into structural and functional diversity. Curr Opin Struct Biol. 2001;11(1):39–46.

43. Thirumoorthy N, et al. A review of metallothionein isoforms and their role in pathophysiology. World J Surg Oncol. 2011;9:54.

44. Li T, et al. TIMER2.0 for analysis of tumor-infiltrating immune cells. Nucleic Acids Res. 2020;48(W1):W509–14.

45. Wang Y et al. Regulator of G Protein Signaling 20 correlates with long intergenic non-coding RNA (lincRNAs) harboring oncogenic potential and is markedly upregulated in Hepatocellular Carcinoma. Biology (Basel), 2022. 11(8).

46. Taniguchi K, Karin M. NF-kappaB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol. 2018;18(5):309–24.

47. Xia L, et al. Role of the NFkappaB-signaling pathway in cancer. Onco Targets Ther. 2018;11:2063–73.

48. Kim MJ, et al. FFAR2 antagonizes TLR2- and TLR3-induced lung cancer progression via the inhibition of AMPK-TAK1 signaling axis for the activation of NF-kappaB. Cell Biosci. 2023;13(1):102.

49. Huang CL, et al. Visfatin upregulates VEGF-C expression and lymphangiogenesis in esophageal cancer by activating MEK1/2-ERK and NF-kappaB signaling. Aging. 2023;15(11):4774–93.

50. Yang CJ, et al. Fluoxetine inactivates STAT3/NF-kappaB signaling and promotes sensitivity to cisplatin in bladder cancer. Biomed Pharmacother. 2023;164:114962.

51. Rascio F et al. The pathogenic role of PI3K/AKT pathway in Cancer Onset and Drug Resistance: an updated review. Cancers (Basel), 2021. 13(16).

52. Yang J, et al. Targeting PI3K in cancer: mechanisms and advances in clinical trials. Mol Cancer. 2019;18(1):26.

53. He Y, et al. Targeting PI3K/Akt signal transduction for cancer therapy. Signal Transduct Target Ther. 2021;6(1):425.

54. Cheng Z, et al. SOX9-transacted long non-coding RNA NEAT1 promotes the self-renewal of liver cancer stem cells through PKA/Hippo signaling. Signal Transduct Target Ther. 2021;6(1):87.

55. Lu Y, et al. Epigenetic regulation in human cancer: the potential role of epidrug in cancer therapy. Mol Cancer. 2020;19(1):79.

56. Nasir A, et al. Nutrigenomics: epigenetics and cancer prevention: a comprehensive review. Crit Rev Food Sci Nutr. 2020;60(8):1375–87.

57. Tulsyan S, et al. Molecular basis of epigenetic regulation in cancer diagnosis and treatment. Front Genet. 2022;13:885635.

58. Loscalzo J, Handy DE. Epigenetic modifications: basic mechanisms and role in cardiovascular disease (2013 Grover Conference series). Pulm Circ. 2014;4(2):169–74.

59. Lin NC, et al. The relation between NEAT1 expression level and survival rate in patients with oral squamous cell carcinoma. J Dent Sci. 2022;17(1):361–7.

60. He K, et al. LncRNA NEAT1 mediates progression of oral squamous cell carcinoma via VEGF-A and notch signaling pathway. World J Surg Oncol. 2020;18(1):261.

61. Liu X, Shang W, Zheng F. Long non-coding RNA NEAT1 promotes migration and invasion of oral squamous cell carcinoma cells by sponging microRNA-365. Exp Ther Med. 2018;16(3):2243–50.

62. Coon J, Kingsley K, Howard KM. miR-365 (microRNA): potential biomarker in oral squamous cell Carcinoma exosomes and Extracellular vesicles. Int J Mol Sci, 2020. 21(15).

63. Huang WC, et al. A novel miR-365-3p/EHF/keratin 16 axis promotes oral squamous cell carcinoma metastasis, cancer stemness and drug resistance via enhancing beta5-integrin/c-met signaling pathway. J Exp Clin Cancer Res. 2019;38(1):89.

64. Zhao J, et al. Construction of a specific SVM classifier and identification of molecular markers for lung adenocarcinoma based on lncRNA-miRNA-mRNA network. Onco Targets Ther. 2018;11:3129–40.

65. Wang RP, et al. Increased long noncoding RNA LINC00511 is correlated with poor prognosis and contributes to cell proliferation and metastasis by modulating miR-424 in hepatocellular carcinoma. Eur Rev Med Pharmacol Sci. 2019;23(8):3291–301.

66. Gou X, Zhao X, Wang Z. Long noncoding RNA PVT1 promotes hepatocellular carcinoma progression through regulating miR-214. Cancer Biomark. 2017;20(4):511–9.

67. Kong Q, et al. The lncRNA MIR4435-2HG is upregulated in hepatocellular carcinoma and promotes cancer cell proliferation by upregulating miRNA-487a. Cell Mol Biol Lett. 2019;24:26.

68. Ding S, et al. LncRNA BCYRN1/miR-490-3p/POU3F2, served as a ceRNA network, is connected with worse survival rate of hepatocellular carcinoma patients and promotes tumor cell growth and metastasis. Cancer Cell Int. 2020;20:6.

69. Wang L, et al. Long non-coding RNA MAPKAPK5-AS1/PLAGL2/HIF-1alpha signaling loop promotes hepatocellular carcinoma progression. J Exp Clin Cancer Res. 2021;40(1):72.

70. Zhang Q, Sjogren B. Palmitoylation of RGS20 affects Galpha(o)-mediated signaling independent of its GAP activity. Cell Signal. 2023;107:110682.

71. Andreou M et al. Prognostic factors influencing survival in Ovarian Cancer patients: a 10-Year retrospective study. Cancers (Basel), 2023. 15(24).

72. Zhao C, et al. CSRP1 gene: a potential novel prognostic marker in acute myeloid leukemia with implications for immune response. Discov Oncol. 2024;15(1):248.

73. Tsukasaki K, et al. Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol. 2009;27(3):453–9.

74. Zhang P, et al. DLAT is a promising prognostic marker and therapeutic target for hepatocellular carcinoma: a comprehensive study based on public databases. Sci Rep. 2023;13(1):17295.

75. Akbari M, et al. CD133: an emerging prognostic factor and therapeutic target in colorectal cancer. Cell Biol Int. 2020;44(2):368–80.

76. Suraweera A, et al. Defining COMMD4 as an anti-cancer therapeutic target and prognostic factor in non-small cell lung cancer. Br J Cancer. 2020;123(4):591–603.

77. Kunitomi H, et al. LAMC1 is a prognostic factor and a potential therapeutic target in endometrial cancer. J Gynecol Oncol. 2020;31(2):e11.

78. Taylor P, et al. REST is a novel prognostic factor and therapeutic target for medulloblastoma. Mol Cancer Ther. 2012;11(8):1713–23.

79. Yu J, et al. Establishment of a Lymph Node Metastasis-Associated Prognostic Signature for lung adenocarcinoma. Genet Res (Camb). 2023;2023:p6585109.

80. Wu J, et al. A novel immunodiagnosis panel for hepatocellular carcinoma based on bioinformatics and the autoantibody-antigen system. Cancer Sci. 2022;113(2):411–22.
81. Li Q, et al. Regulator of G protein signaling 20 correlates with clinicopathological features and prognosis in triple-negative breast cancer. Biochem Biophys Res Commun. 2017;485(3):693–7.
82. Yuan G, et al. RGS12 inhibits the progression and metastasis of multiple myeloma by driving M1 macrophage polarization and activation in the bone marrow microenvironment. Cancer Commun (Lond). 2022;42(1):60–4.
83. Schwable J, et al. RGS2 is an important target gene of Flt3-ITD mutations in AML and functions in myeloid differentiation and leukemic transformation. Blood. 2005;105(5):2107–14.
84. Fong CW, et al. Specific induction of RGS16 (regulator of G-protein signalling 16) mRNA by protein kinase C in CEM leukaemia cells is mediated via tumour necrosis factor alpha in a calcium-sensitive manner. Biochem J. 2000;352(Pt 3):747–53.
85. Carreras J, et al. Clinicopathological characteristics and genomic profile of primary sinonasal tract diffuse large B cell lymphoma (DLBCL) reveals gain at 1q31 and RGS1 encoding protein; high RGS1 immunohistochemical expression associates with poor overall survival in DLBCL not otherwise specified (NOS). Histopathology. 2017;70(4):595–621.
86. Qin J, et al. Systematic discrimination of the repetitive genome in proximity of ferroptosis genes and a novel prognostic signature correlating with the oncogenic lncRNA CRNDE in multiple myeloma. Front Oncol. 2022;12:1026153.
87. Yahiaoui OI, et al. Constitutive AKT activation in follicular lymphoma. BMC Cancer. 2014;14:565.
88. Serrat N, et al. PI3Kdelta inhibition reshapes follicular lymphoma-immune microenvironment cross talk and unleashes the activity of venetoclax. Blood Adv. 2020;4(17):4217–31.
89. Dou R, et al. Suppression of steroid 5alpha-reductase type I promotes cellular apoptosis and autophagy via PI3K/Akt/mTOR pathway in multiple myeloma. Cell Death Dis. 2021;12(2):206.
90. Yang N, et al. LncRNA OIP5-AS1 loss-induced microRNA-410 accumulation regulates cell proliferation and apoptosis by targeting KLF10 via activating PTEN/PI3K/AKT pathway in multiple myeloma. Cell Death Dis. 2017;8(8):e2975.
91. Bloedjes TA, et al. AKT supports the metabolic fitness of multiple myeloma cells by restricting FOXO activity. Blood Adv. 2023;7(9):1697–712.
92. Hsu J, et al. The AKT kinase is activated in multiple myeloma tumor cells. Blood. 2001;98(9):2853–5.
93. Jiang F, et al. HNRNPA2B1 promotes multiple myeloma progression by increasing AKT3 expression via m6A-dependent stabilization of ILF3 mRNA. J Hematol Oncol. 2021;14(1):54.
94. Frenquelli M, et al. The WNT receptor ROR2 drives the interaction of multiple myeloma cells with the microenvironment through AKT activation. Leukemia. 2020;34(1):257–70.
95. Hu N, et al. Follicular lymphoma-associated BTK mutations are inactivating resulting in augmented AKT activation. Clin Cancer Res. 2021;27(8):2301–13.
96. Ramos-Campoy O, et al. Differential Gene expression in sporadic and genetic forms of Alzheimer's Disease and Frontotemporal Dementia in Brain tissue and lymphoblastoid cell lines. Mol Neurobiol. 2022;59(10):6411–28.
97. Hu H, et al. Genome-wide association study identified ATP6V1H locus influencing cerebrospinal fluid BACE activity. BMC Med Genet. 2018;19(1):75.
98. McAllister CE, et al. GPER1 stimulation alters posttranslational modification of RGSz1 and induces desensitization of 5-HT1A receptor signaling in the rat hypothalamus. Neuroendocrinology. 2014;100(2–3):228–39.
99. Creech RD, et al. Estradiol induces partial desensitization of serotonin 1A receptor signaling in the paraventricular nucleus of the hypothalamus and alters expression and interaction of RGSZ1 and galphaz. Neuropharmacology. 2012;62(5–6):2040–9.
100. Sharma A, et al. Marginalizing the genomic architecture to identify crosstalk across cancer and neurodegeneration. Front Mol Neurosci. 2023;16:1155177.

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