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REVIEW

A Review of the Role and Mechanism of GNG4 Gene Expression in the Tumor Microenvironment Across Broad Spectrum of Tumor Types

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Abstract: DNA methylation is a common and very important type of epigenetic modification, and its changes often occur in cancer and are highly dysregulated. Guanine Nucleotide binding-protein Gamma subunit 4 (GNG4), as a key component of the G protein-coupled receptor (GPCR) signaling pathway, its methylation is closely related to the occurrence and development of various tumors. The immuno-suppressive state and component remodeling of the tumor microenvironment (TME) are the core driving factors for tumor progression, and GNG4 plays a-dimensional role in regulating TME by regulating signaling pathway activity, immune cell infiltration and microenvironmental physical and chemical characteristics. This review comprehensively summarizes the expression pattern of GNG4 in different tumors, analyzes its regulatory mechanism on immune cells, signaling molecules and pathological characteristics in TME, and explores its clinical potential as a prognostic marker and therapeutic target providing references for broad spectrum of tumors research and precision treatment.

Keywords: GNG4, prognosis, tumor

Methods: Literature Search and Selection

A systematic literature search was conducted to identify studies investigating the role of GNG4 in the tumor microenvironment across different cancer types. The PubMed and Web of Science databases were searched from inception to November 2025, using the following search terms in combination: "GNG4", "G protein subunit gamma 4", "tumor microenvironment", "immune infiltration", "prognosis", "DNA methylation", and "GPCR signaling." Additional records were identified through manual screening of reference lists from relevant articles.

Studies were included if they met the following criteria: (1) original research articles or published reviews that directly investigated GNG4 expression, function, or regulation; (2) studies examining the relationship between GNG4 and tumor prognosis or TME characteristics; (3) articles published in English in peer-reviewed journals. Studies were excluded if: (1) GNG4 was only mentioned as one of numerous differentially expressed genes in broad screening analyses without specific investigation; (2) the main topic was not related to GNG4 or GPCR-G protein signaling in cancer; (3) full text was unavailable.

A total of 86 records were initially retrieved, of which 24 were selected for full-text review based on title and abstract screening. The final selection comprised 11 studies, including 9 original research articles directly investigating GNG4 expression, prognostic value, and its regulatory role in the tumor microenvironment across glioblastoma, colorectal cancer, lung adenocarcinoma, osteosarcoma, and bladder cancer, as well as 2 review articles providing foundational context on GPCR and G-protein signaling pathways.

The Structure and Biological Function of GNG4 Gene

G protein subunit gamma 4 (GNG4), one of the fourteen gamma subunits of human G protein, which is necessary for GTPase activity, GTP substitution for GDP, and G protein effector interaction.[1] GNG4 could form a complex with the α

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subunit and the β subunit, regulating the downstream signal transduction of GPCR by binding GTP/GDP. G protein transduces information via multiple signal pathways, including PI3K, MAPK, as well as RhoGEF pathways.[1–3]

Under normal physiological conditions, GNG4 participates in the precise regulation of cell proliferation, migration, and immune response, and its function depends on combination with specific β subunits and the selective activation of downstream effector molecules. In the tumor background, the expression of GNG4 is often regulated by epigenetic mechanisms such as significant down-regulation of expression due to DNA hypermethylation in glioblastoma, while it shows an upward trend of expression in solid tumors such as colorectal cancer and lung cancer. This differential expression pattern suggests that GNG4 may exert context-dependent functions in different tumor types, potentially acting as a tumor suppressor in some cancers while promoting progression in others, though the underlying mechanisms remain to be fully elucidated.

The Expression Characteristics of GNG4 Across Multiple Tumor Types

Correlation Between Expression Differences and Tumor Types

Many kinds of tumors analysis that GNG4 expression levels were significantly higher in most human tumor tissues than in paired normal tissues, but its expression pattern exhibited tumor specificity. In glioblastoma (GBM), GNG4 was significantly downregulated due to high methylation in the promoter region,[1] and the silencing was more obvious in the mesenchymal subtype. However, in colorectal cancer (CRC)[4–6,] lung adenocarcinoma,[7,8] osteosarcoma,[9] and bladder cancer (BLCA),[10,11] GNG4 was expressed an increased level, and high expression was associated with an increase in tumor malignancy. This difference of expression may be related to the differentiation state of tumor cells, subtype characteristics, microenvironmental signals, such as signals from the hypoxic microenvironment of lung adenocarcinoma, which may contribute to the upregulation of GNG4 expression.[7,8]

Correlation Between Expression Level and Clinical Prognosis

The expression level of GNG4 has been demonstrated to serve as an independent prognosis indicator for various types of tumors. In colorectal cancer, high GNG4 expression was significantly associated with a shorter overall survival (OS) and disease-free survival (DFS) and was positively correlated with lymph node metastasis and clinical stage.[4–6] In adenocarcinoma of lung cancer and osteosarcoma patients, high GNG4 expression similarly predicted poor prognosis, and its expression level could effectively distinguish high-risk populations from those low-risk ones.[7–9] While in glioblastoma, the epigenetic silencing of GNG4 closely associated with tumor progression and a reduced patient survival rate, which suggesting that the loss of its tumor-suppressive function may lead to disease progression.[1]

The Core Mechanisms of GNG4 Regulating the Tumor Microenvironment

Microenvironment Remodeling Mediated by Signaling Pathways

GNG4 regulates the formation and function of TME by regulating crucial signaling pathways. In glioblastoma, the restoration of GNG4 expression significantly inhibits the activity of SDF1α/CXCR4 signaling pathway, thus reducing the phosphorylation of downstream pERK and pJNK, thereby suppressing the migration of tumor cells as well as the invasion ability of mesenchymal subtype.[1] And the inhibition of this pathway can indirectly affect the chemotactic recruitment of tumor-associated macrophages. In colorectal cancer, GNG4 regulates the immune-related signaling network, promoting the transformation of TME to an immuno-suppressive phenotype, and its expression is correlated with the expression of immune checkpoint molecules (ICPs), weakening the anti-tumor immune response.[4–6] In addition, preliminary evidence in colorectal cancer suggests that GNG4 may regulate the secretion of angiogenesis-related factors through GPCR signaling, thereby affecting the blood supply and nutritional status of the TME; however, this mechanism has not been confirmed across a broad range of tumors.[4]

The Regulatory Role of GNG4 in Immune Cell Infiltration

The alteration of immune cell infiltration pattern is one of the core effects of GNG4 regulating TME. For example, in colorectal cancer, high expression of GNG4 is associated with a significant decrease in the number of tumor-infiltrating immune cells, such as CD8 cytotoxic T cells and CD4 helper T cells. At the same time, accompanied by increasing in the proportion of immuno-suppressive cells, such as regulatory T cells and myeloid-derived suppressive cells.[4–6] In result, forming an immune desert microenvironment. In bladder cancer, GNG4 is specifically expressed in exhausted CD4 T cells, and its high expression is associated with an increased level of total immune cell infiltration; however, the infiltrating cells are mainly functionally exhausted, and this unique infiltration pattern may help predict response to immunotherapy.[10,11] These tumor-specific differences in immunoregulation may originate from the differences in the interaction of GNG4 with different surface receptors.

Correlation with Pathological Characteristics of Microenvironment

The expression of GNG4 is closely associated with key pathological characteristics of TME. Broad types of cancer analysis show that the level of GNG4 expression is significantly correlated with tumor mutation burden (TMB), microsatellite instability (MSI), and the number of neoantigens, which are important factors affecting the sensitivity of immunotherapy.[6,10,11] In lung adenocarcinoma, GNG4 expression appears to be associated with hypoxia-related signaling, and its upregulation may further influence the activation of the hypoxia-inducible factor (HIF) pathway, potentially contributing to a positive regulatory cycle that aggravates the hypoxic state and metabolic reprogramming of the TME.[7,8] In bladder cancer, GNG4 expression can distinguish the TME characteristics of different molecular subtypes. High GNG4 expression is consistent with the immune infiltration characteristics of basal-like subtype, and low expression is related to the inflammatory microenvironment of luminal-like subtype.

The Clinical Translation Potential of GNG4

Prognostic Evaluation Biomarker

The expression pattern of GNG4 provides an effective tool for prognostic evaluation across many tumor types. In colorectal cancer, the integration of GNG4 expression with the characteristics of immune infiltration can construct a prognostic model, which exhibits superior prediction efficacy than traditional clinical indicators. In the bladder cancer, current study confirms that the expression of GNG4 can be combined with TMB and MSI status for further improving the accuracy of prognostic stratification. While in glioblastoma, the methylation status of GNG4 can be used as an epigenetic biomarker for diagnosis and subtype distinction.

Therapeutic Response and Prediction Value

GNG4 has shown significant potential in guiding the selection of tumor treatment regimens. In bladder cancer, high GNG4 expression predicts a better response to immune checkpoint inhibitors (ICB) therapy, while low expression patients are more likely to benefit from chemotherapy[10,11].Similarly, emerging evidence suggests that GNG4 expression levels may be associated with the objective response rate of ICB treatment in colorectal cancer.[4–6] In addition, in glioblastoma, demethylation therapy targeting GNG4 methylation may restore its tumor-suppressive function, providing a new strategy reversing the aggressive mesenchymal subtype.

Prospects for Therapeutic Target Development

The signaling pathways regulated by GNG4 provide potential targets for drug development. In glioblastoma, therapeutic strategies targeting the GNG4-SDF1α/CXCR4 axis may help suppress tumor invasion and TME remodeling. In colorectal cancer, modulation of GNG4 expression or its downstream pathways could potentially reverse the immuno-suppressive TME and enhance the efficacy of ICB treatment, though this remains to be validated in preclinical and clinical studies. However, it is important to alert the functional heterogeneity of GNG4 in different tumors. As a result, tumor-specific therapeutic regimens need to be designed based on its expression pattern and mechanisms in different kinds of tumors.

Current Status and Perspective

Currently, research on GNG4 and TME still has many limitations. First, the mechanism of the tumor-suppressing and oncogenic functions of GNG4 in different tumors is still not clear, which now considered may be closely related to the tumor cell type and microenvironment signaling background. Second, there is still insufficient research on the molecular details of GNG4 regulating the function of immune cells. Third, clinical translation research is mostly based on bioinformatics analysis, lacking of prospective clinical trial validation. Future research should focus on elucidating the upstream regulatory networks and downstream effector molecules of GNG4 in the tumor types where its role has been most clearly demonstrated namely glioblastoma, colorectal cancer, and lung adenocarcinoma. Single-cell sequencing and spatial transcriptomics approaches will be particularly valuable for clarifying the cell-specific functions of GNG4 within the TME. At the same time, clinical trials should be conducted to promote its application in precision diagnosis and treatment.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this research.

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The author(s) declares that no Generative AI was ever used in the creation of this manuscript.

Disclosure

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