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Roles of GNA13 in Various Types of Cancer

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ABSTRACT

GNA13, a component of the G protein signaling network, is involved in regulating cancer cell growth, migration, and programmed cell death. Recent evidence has shown increased levels of GNA13 across several tumor types, including breast, prostate, stomach, and liver cancers, closely linking its expression to tumor progression, spread, and patient outcomes. This article systematically reviews GNA13 expression across diverse cancers and explores its functional impact on tumor biology. Particular attention is given to the pathways through which GNA13 enhances cancer progression, specifically by stimulating AKT, ERK, and MYC signaling and suppressing FOXO1. Current research identifies GNA13 as an emerging biomarker and potential target for cancer diagnosis and therapy, paving the way for future treatment innovations.

KEYWORDS

GNA13; G protein; Tumor progression; AKT signaling pathway; MYC

1 Significance of the study

GNA13 (G protein subunit alpha 13) is an essential element within the G protein signaling system, significantly contributing to key cellular activities including cell growth, migration, and apoptosis. Accumulating evidence reveals that elevated GNA13 expression occurs in multiple malignancies, especially breast, prostate, and gastric cancers, all noted for their high mortality. At the molecular level, GNA13 promotes tumor cell growth and invasion by triggering the AKT and ERK signaling cascades, increasing c-Myc function, and suppressing FOXO1 activity, suggesting its value as a promising therapeutic candidate for cancer intervention.

This study aims to systematically investigate the expression profile of GNA13 protein across different cancer types and explore its influence on tumor biological behavior, thus elucidating its pivotal role in tumor initiation, progression, and metastasis. By examining the mechanisms by which GNA13 contributes to various cancers, this study will not only deepen the understanding of cancer signaling pathways but also offer novel insights and potential targets for cancer diagnosis and therapy. Ultimately, this research may drive the development of personalized therapeutic strategies targeting GNA13 in the future.

2 Review of Research Status at Home and Abroad

2.1 Basic Information of GNA13 and Its Role in G Protein Signaling Transduction

GNA13, alternatively referred to as G protein alpha-13 subunit, is a key part of the heterotrimeric G protein family. It plays a vital role in transmitting intracellular signals and is involved in multiple physiological and pathological events. By interacting with G protein-coupled receptors (GPCRs), GNA13 acts as a molecular regulator that transmits external signals into cells, triggering the activation of various downstream effectors. [1]Through modulating small GTPases such as RhoA, GNA13 influences multiple cellular functions including proliferation, migration, and apoptosis. [2]Additionally, GNA13-mediated signaling is closely associated with processes such as cytoskeletal reorganization, inflammatory responses, and tumorigenesis, making it a pivotal factor in cellular functions and disease progression.[3]

2.2 The Importance of GNA13 in Cancer Research

In recent years, the significance of GNA13 in cancer research has become increasingly prominent. The therapeutic potential of GNA13 as a target is also gaining recognition. Regulating the activity of GNA13 or its downstream signaling pathways may provide new strategies for cancer treatment. For example, targeted intervention in specific GNA13-associated pathways could effectively inhibit cancer cell proliferation and metastasis. [4]Therefore, an in-depth investigation of GNA13's functions and its specific roles in cancer could facilitate the development of personalized medicine and novel therapeutic approaches, bringing new hope to cancer patients.

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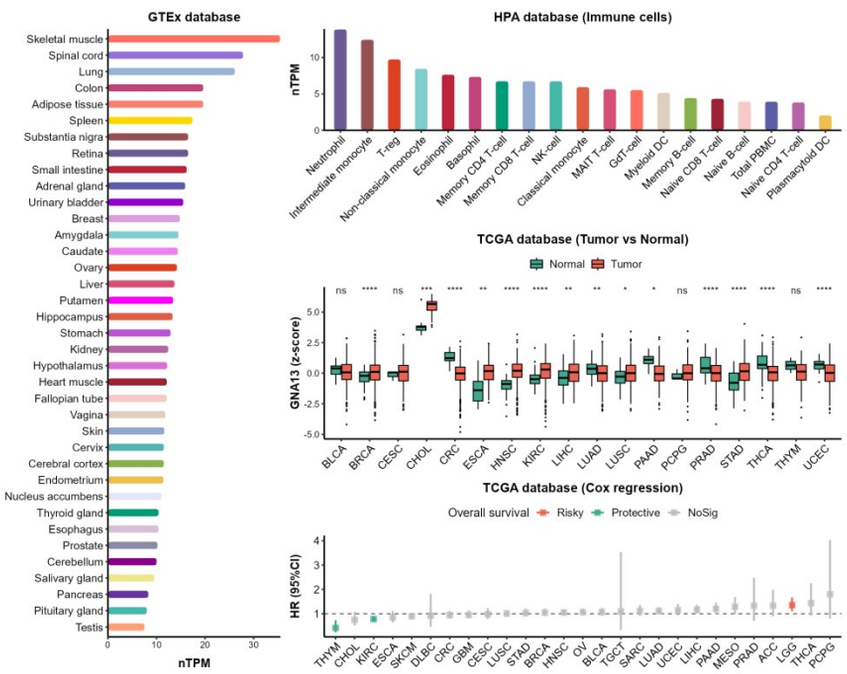
3 Structure of GNA13

G proteins are members of an intracellular protein family that function as mediators of proliferation, differentiation, and apoptosis in various cell types. They consist of three subunits: Gα, Gβ, and Gγ. The Gα subunits can be further subdivided into four subfamilies: Gq (including Gα14, Gα11, Gαq), Gi (including Gαi1, Gαi2, Gαi3, GαoA, GαoB, Gαt1, Gαt2, Gαz), Gs (including Gαs and Gαolf), and G12 (including Gα12 and Gα13, encoded by the GNA12 and GNA13 genes, respectively).



As shown in the figure, the GNA13 gene exhibits significant differences in expression and prognostic impact across multiple cancer types. In the comparison between tumor and normal tissues from the TCGA database, GNA13 expression is significantly upregulated in breast cancer (BRCA), colorectal cancer (COAD), and cervical cancer (CESC) ($p<0.05$), while no significant difference (ns) is observed in certain cancer types such as liver cancer (LIHC) and gastric cancer (STAD).

Moreover, Cox regression analysis revealed that GNA13 significantly increases the risk of overall survival in liver cancer (LIHC) patients (HR>1), indicating it is a risk factor in this cancer type. In contrast, GNA13 exhibits a protective effect (HR< 1) in kidney renal clear cell carcinoma (KIRC), correlating with improved survival rates. However, in cancer types such as lung adenocarcinoma (LUAD) and gastric cancer (STAD), GNA13 shows no significant association (NoSig) with overall survival.

3.1 Breast Cancer

GNA13 has subtype-specific roles in breast cancer. Through survival analysis using the KMplotter platform, Subramanyan's research team observed that elevated expression of GNA13 correlated significantly with improved prognosis in certain breast cancer patient subsets. Further experiments indicated cell-line dependent regulatory roles: in MCF-7 and ZR-75-1 cells characterized by naturally high GNA13 levels, knockdown of GNA13 led to increased transcription and protein expression of MYC, along with enhanced activation of its downstream pathways. In contrast, overexpression of GNA13 in T47D cells, which normally exhibit low endogenous GNA13 expression, selectively suppressed a specific MYC isoform involved in carcinogenesis and proliferation driven by MYC. These observations imply a critical role for Gα13 in breast cancer progression through MYC modulation.

Additionally, chromatin immunoprecipitation (ChIP) assays revealed that induction of GNA13 increased the binding of the NF-κB subunit p65 to the CXCL5 promoter region. GNA13 knockdown diminished p65 phosphorylation and reduced NF-κB signaling activity, while depletion of p65 partially counteracted the GNA13-induced upregulation of CXCL5.

Furthermore, the team investigated Gα13's impact on proliferation in ER-positive (T47D, MCF7, ZR-75-1) and ER-negative (SKBR3, MDA-MB-231) breast cancer cell lines. Knockdown of GNA13 significantly promoted proliferation, while its re-expression reversed this effect. Specifically, introducing GNA13 into T47D cells with low intrinsic expression considerably inhibited cell growth. Anchorage-independent growth assays demonstrated increased colony-forming ability upon GNA13 knockdown, further supporting its tumor-suppressive role. Conversely, introducing GNA13 into T47D

cells markedly reduced colony formation capability, reaffirming its critical inhibitory effect on cell proliferation in ER-positive breast cancer subtypes.

Moreover, in MCF-7 and ZR-75-1 cells, which exhibit high GNA13 expression, knockdown of GNA13 resulted in significantly elevated MYC expression. Further analyses showed that GNA13 overexpression inhibited the activities of both MYC and E2F signaling pathways.[5]

3.2 Prostate Cancer

In prostate cancer, high levels of GNA13 expression facilitate tumor formation, enhance drug resistance, and increase cancer cell invasiveness. Inhibition of GNA13 expression or its signaling activity has been shown to effectively reduce these malignant properties. Studies have demonstrated that GNA13 modulates the transcriptional activity of the CXCL5 promoter, significantly affecting CXCL5 expression. Specifically, Lim's group utilized luciferase assays and found that suppressing GNA13 markedly reduced the activity of the CXCL5 promoter region, especially at the −505/+62 site, suggesting it as a critical regulatory element for GNA13-mediated transcriptional control. Conversely, overexpression of GNA13 in LnCaP cells substantially elevated CXCL5 promoter activity, again most notably within the −505/+62 region. Furthermore, GNA13-driven CXCL5 expression was shown to depend on the activation of Rho signaling; pharmacological inhibition of Rho significantly reduced GNA13-induced CXCL5 mRNA levels in prostate cancer cells, revealing Rho signaling as an essential downstream effector of GNA13's oncogenic activity.[6]

3.3 Head and Neck Squamous Cell Carcinoma (HNSCC)

In head and neck squamous cell carcinoma (HNSCC), increased expression of GNA13 promotes tumor drug resistance and invasiveness. Epithelial-mesenchymal transition (EMT) enables epithelial cells to acquire mesenchymal characteristics, thereby enhancing cell migration and invasiveness, and is closely associated with tumor-initiating cell (TIC) properties. Research by S. A. K. Rasheed's group demonstrated that elevated GNA13 levels induce gene expression changes consistent with an EMT phenotype. When comparing spheroid cultures with monolayer cultures, NCC-HN43 and NCC-HN26 cells cultured under spheroid conditions exhibited significantly increased expression of TIC markers and GNA13, indicating that GNA13 plays a pivotal role in drug resistance in HNSCC.

Additionally, Rasheed's team found that knockdown of GNA13 reduced the phosphorylation levels of c-Jun (JNK pathway), ERK1/2 (RAS-RAF-MAPK pathway), and IκB (NFκB pathway). Inhibition of these signaling pathways (using NFκB inhibitor BAYi, JNK inhibitor JNKi, and MEK inhibitor MEKi) significantly decreased the expression of TIC markers such as $CD24^{-}/CD44^{+}$ and ALDH1, diminished spheroid-forming capability, and reversed GNA13-induced cisplatin resistance, restoring treatment sensitivity in resistant cells.

The high expression of GNA13 promotes epithelial-mesenchymal transition (EMT) and drug resistance. Overexpression of GNA13 is associated with resistance to cytotoxic therapies, including cisplatin and ionizing radiation, whereas knockdown of GNA13 enhances cancer cell sensitivity to treatment. Furthermore, GNA13 may serve as a potential prognostic biomarker, particularly in head and neck squamous cell carcinoma (HNSCC), where its detection through immunohistochemistry (IHC) can help identify high-risk patient populations.[7]

3.4 Gastric Cancer

In gastric cancer, experimental studies have shown that artificially increasing the expression of GNA13 in cell lines such as AGS and HGC-27—both characterized by inherently low GNA13 expression—markedly accelerated their proliferation, as demonstrated by assays including MTT and colony formation. In contrast, reducing GNA13 levels significantly impaired the proliferative abilities of these cell lines, emphasizing its essential function in regulating gastric cancer cell growth in vitro. Furthermore, GNA13 has been found to drive gastric cancer progression via activation of key signaling pathways such as PI3K/AKT/FOXO1 and MAPK/ERK/FOXO1, and by enhancing c-Myc-mediated transcriptional activities. These pathways collectively provide a mechanistic framework to understand how GNA13 contributes to gastric carcinogenesis and tumor advancement.[8]

3.5 Hepatocellular Carcinoma (HCC)

In the study conducted by the J.X.Z. group focusing on hepatocellular carcinoma (HCC), it was found that although overexpression of GNA13 did not significantly enhance HCC cell proliferation, it markedly increased cell invasiveness. Using Western blot and qPCR assays, the team determined that protein and mRNA levels of GNA13 were significantly higher in HCC tissues compared to adjacent non-cancerous tissues. Among 12 pairs of HCC samples, 10 exhibited elevated GNA13 expression, achieving statistical significance ($P = 0.006$). Immunohistochemical analysis of 246 paired

HCC and adjacent non-cancerous tissues revealed high GNA13 expression in 60.2% (148/246) of HCC samples, primarily localized in the cytoplasm of cancer cells.

Clinically, high GNA13 expression was significantly associated with tumor multiplicity. Kaplan-Meier survival analysis indicated that patients with high GNA13 expression had significantly shorter median overall survival (OS) compared to the low-expression group. The research from the J.X.Z. group confirmed that GNA13 plays a critical role in promoting cellular invasiveness in HCC. Experiments using HepG2 and SMMC-7721 cell lines showed that although overexpression of GNA13 did not significantly affect proliferation, it significantly enhanced cell invasion capability. This observation was confirmed through invasion assays, suggesting that GNA13 primarily contributes to HCC progression via invasion-related molecular mechanisms.

Additionally, results from Western blot indicated that increased expression of GNA13 had no notable effect on phosphorylated AKT (P-AKT) and ERK (P-ERK) levels. Clinical data analysis demonstrated a significant correlation between elevated GNA13 expression and multiple clinical parameters, including tumor multiplicity, higher TNM classification, and advanced BCLC stage. Survival analyses using Kaplan-Meier curves and Cox regression further established that high expression of GNA13 independently predicted poorer overall survival (OS) and disease-free survival (DFS), especially in patients with tumors exceeding 5 cm in size, advanced TNM stages (III/IV), and higher pathological grades (III/IV).

These results suggest that GNA13 not only serves as an essential biomarker for prognosis assessment in HCC patients but also has potential as a therapeutic target to prevent invasion and metastasis in future HCC treatment strategies.[9]

4 Conclusion

In summary, GNA13 plays a significant role in tumor initiation, invasion, metastasis, and immune escape across various malignancies. High expression of GNA13 is typically associated with increased tumor aggressiveness and poorer prognosis. GNA13 promotes tumor progression by selectively inhibiting MYC isoforms, activating critical signaling pathways such as Rho GTPase and NF-κB, and regulating cytoskeletal reorganization, epithelial-mesenchymal transition (EMT), and the expression of numerous pro-tumor factors. These observations highlight GNA13 as a valuable potential prognostic biomarker and therapeutic target.

Further research is needed, given the existing gaps in understanding the precise mechanisms by which GNA13 influences cancer progression. Future studies may focus on these unknown aspects to gain deeper insights. Additionally, targeting GNA13 or its downstream signaling pathways could emerge as an effective anticancer strategy. In specific cancers, such as breast cancer, enhancing GNA13 expression could suppress tumor cell proliferation. These strategies offer novel possibilities for the development of future therapeutic interventions.

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