Molecular Cancer

REVIEW

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Contract to kill: GNAS mutation

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Abstract

The mutation in Gsα-coding *GNAS* exons, popular as gsp oncogene, is the most frequent mutation across all heterotrimeric G proteins involved in oncogenesis. *GNAS* R201, the most frequently mutated, followed by Q227, are found predominantly across various neoplasms and cancers such as IPMN, pituitary, thyroid, appendiceal, colorectal, etc. This review emphasizes the pivotal significance of the gsp oncogene and its ramifications underpinning the sustained addiction to *GNAS* mutation. Recent studies delineating the mechanistic intricacies that provide solid evidence of the profound impact of oncogenic *GNAS* on tumor formation, progression, and maintenance are highlighted. We have leveraged the discoveries of Gsα as an ideal neoantigen candidate for vaccine therapy, allele-specific inhibitors, and cyclic peptide-based small molecular inhibitors for G proteins and explored the therapeutic potential to target oncogenic *GNAS* directly. Alternative therapeutic modalities and patient-centric studies to mitigate the impact of *GNAS* mutations are also discussed. The exposition of novel studies and strategies designed to address the potential challenges inherent in these approaches of targeting the activating mutations of *GNAS*, along with probable avenues for further investigation, are highlighted. This review aims to reverberate the current understanding of the oncogenic potential of *GNAS*, the genomic and biological landscape of *GNAS*-driven neoplasms and cancers, and potential therapeutic strategies against them.

Keywords *GNAS*, Gsα, *GNAS* R201, Mutation, Tumor, Neoplasm

Introduction: structural and functional attributes of *GNAS*

GNAS (guanine nucleotide alpha-stimulating binding protein) is an imprinted gene with the complex locus on the q arm of chromosome 20 [1]. It incorporates four alternative promoters, and its first exon splices onto exon two and encodes multiple transcripts: Gsα (Gs-α long), *GNAS* A/B (Gs-α short), XLαs (extra-long α s), NESPAS, and NESP55 with exons 2–13 in common [1, 2] (Fig. 1). The three transcripts, Gsα, *GNAS* A/B, and XLαs, are isoforms with distinct N-terminals [3]. The second overlapping open reading frame of XL exon 1 encodes another product, ALEX (alternative gene product encoded by XL exon). NESP55 is very distinct from Gsα as it has a stop codon in its first exon, and thus, the entire coding region is located within the first exon itself. The expression of these transcripts is biallelic, paternal, or maternal based on the allele-specific methylation of their promoters on differentially demethylated regions [4] (Fig. 1). Gsα is not methylated and has biallelic expression, with silenced paternal expression in some tissues. NESP55 is methylated in the paternal allele and maternally expressed along with Gsα. Transcripts such as *GNAS* A/B, XLαs, and NESPAS are expressed in the paternal allele as these are methylated in the maternal allele [4].

Delving into the biochemical structure, Gsα, the major product of *GNAS*, comprises a Ras-like domain, which possesses GTPase activity, and the α-helical domain [5]. The nucleotide-binding pocket is located between these two domains and is surrounded by P-loop and switch

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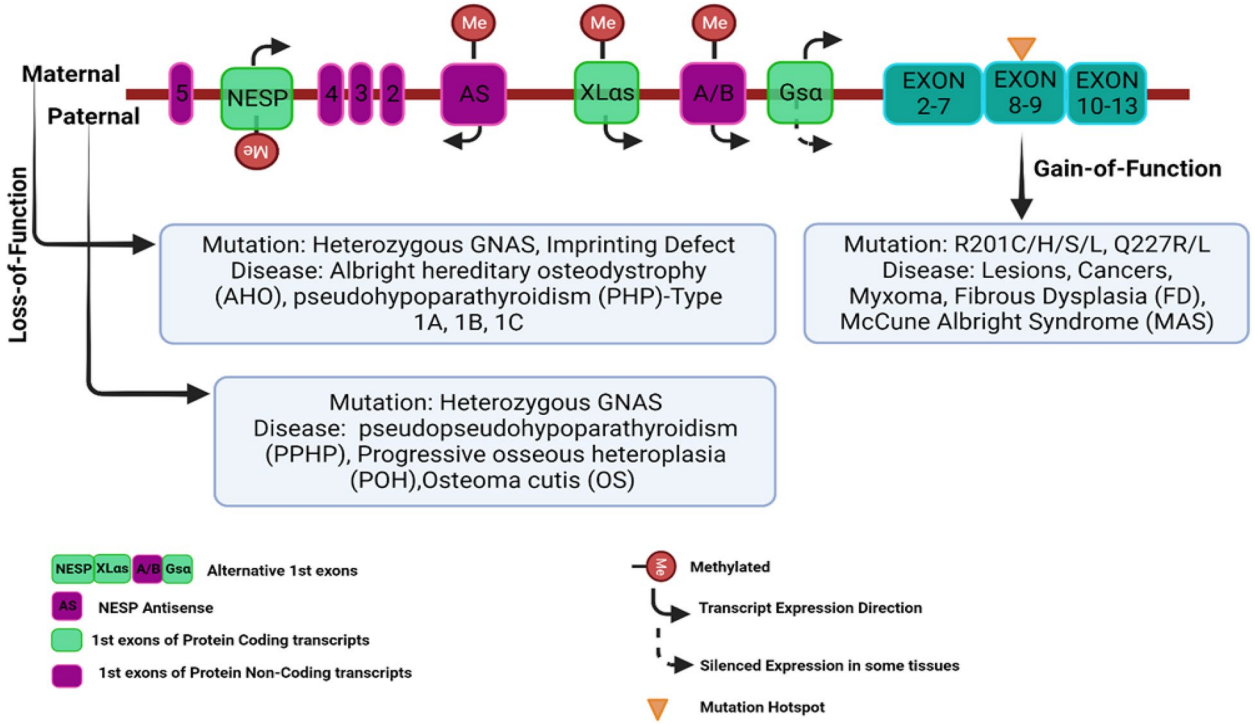

Fig. 1 Structure and Functional attributes of *GNAS* Complex Locus (**A**). *GNAS* is an imprinted gene including 13 exons, with alternative first exons and promoters that encode multiple transcripts: Gsα, *GNAS* A/B, XLαs, NESPAS, and NESP55 with common exons 2–13. Gsα is biallelic, while the other four transcripts are monoallelic and have allele-specific differential methylation of their promoters. The gain or loss of function of GNAS results in various diseases

regions [6] (Fig. 2). Upon the interaction with activated GPCR, the interaction between the P-loop and phosphate group of GDP is disrupted, resulting in significant conformational changes in switch regions [6–8]. This facilitates the destabilization of the GDP binding, dissociation of GDP, and the opening of the nucleotide-binding pocket, thus enhancing the affinity for GTP binding (Fig. 2). The binding of GTP causes further conformational changes,

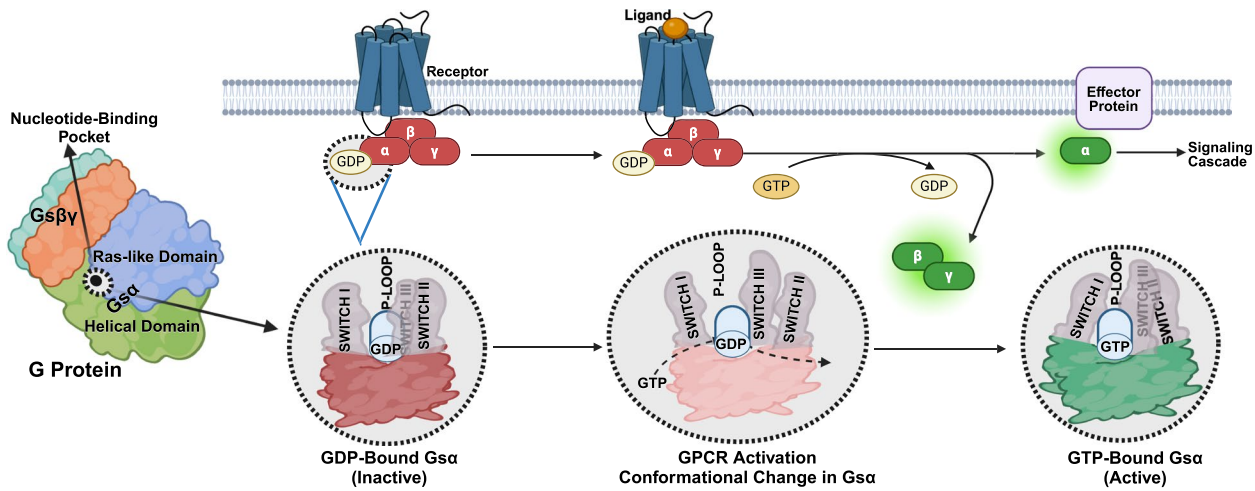

Fig. 2 Structural depiction of activation of Gsα GTPase Switch (**B**). Gsα consists of a Ras-like GTPase domain and an α-helical domain, with a nucleotide-binding pocket between them. Activation by GPCRs disrupts the P-loop interaction with GDP, triggering conformational changes that promote GDP dissociation and GTP binding. This allows Gsα to dissociate from Gβγ subunits and activate effector proteins like adenylyl cyclase, initiating downstream signaling

allowing Gαs to dissociate from the Gβγ subunits and interact with effector proteins like adenylyl cyclase to activate the downstream pathways [5]

Gsα plays a vital role in signal transduction from GPCRs, stimulating the effectors to regulate diverse cellular functions. Hence, proper functioning of Gαs is crucial for maintaining normal cellular responses to external signals, and dysregulation of Gαs signaling can lead to various diseases, including endocrine disorders and cancers [9, 10] (Fig. 1). The loss of function or inactivating mutations in Gsα-coding *GNAS* exons results in pseudohypoparathyroidism Ia, Ib, Ic (PHP-Ia, -Ib, -Ic), pseudopseudohypoparathyroidism (PPHP), Albright hereditary osteodystrophy (AHO), progressive osseous heteroplasia (POH), and osteoma cutis (OC) [11–15]. Diseases such as PPHP, POH, and OS are due to the inactivating heterozygous *GNAS* of paternal origin, while PHP-Ia, PHP-Ic, and AHO are of maternal origin. Further, the imprinting defect: heterozygous deletion of regulatory elements in the maternal *GNAS* results in PHP-Ib [12] The gain of function or activating mutations in *GNAS* causes diseases like fibrosis dysplasia (FD), McCune-Albright syndrome (MAS), and various cancers [9, 10, 16].

GNAS to gsp: unlocking the oncogenic addiction

R201 (Arginine 201) and Q227 (Glutamine 227) are crucial for the function of the Gαs protein in interacting with GTP and coordinating its hydrolysis [10]. The guanidinium group in the side chain of R201 forms hydrogen bonds with the oxygen atoms of the γ-phosphate of GTP, which is essential for stabilizing the γ-phosphate of GTP and thus the switch between active (GTP-bound) and inactive (GDP-bound) states. Additionally, Q227 interacts with the β-phosphate of GTP and stabilizes the GTP-bound state of the Gαs protein. The side chain of glutamine can form hydrogen bonds with the water molecule and is essential for hydrolysis [10]. Mutations in these residues, substituting amino acid R at codon 201 to C/H/S and Q at 227, disrupt regular GTPase activity, such that Gαs protein cannot properly hydrolyze. This leads to a constitutively active form of Gαs, which continuously stimulates downstream signaling pathways, contributing to the disorders and diseases [9, 10, 16]. The codon R201 is the most frequently mutated, followed by codon Q227 in *GNAS*. The mutant form of *GNAS*/ Gsα is known as the gsp oncogene, as it is predominantly found in various neoplasms and cancers (Fig. 3) [17]. *GNAS*

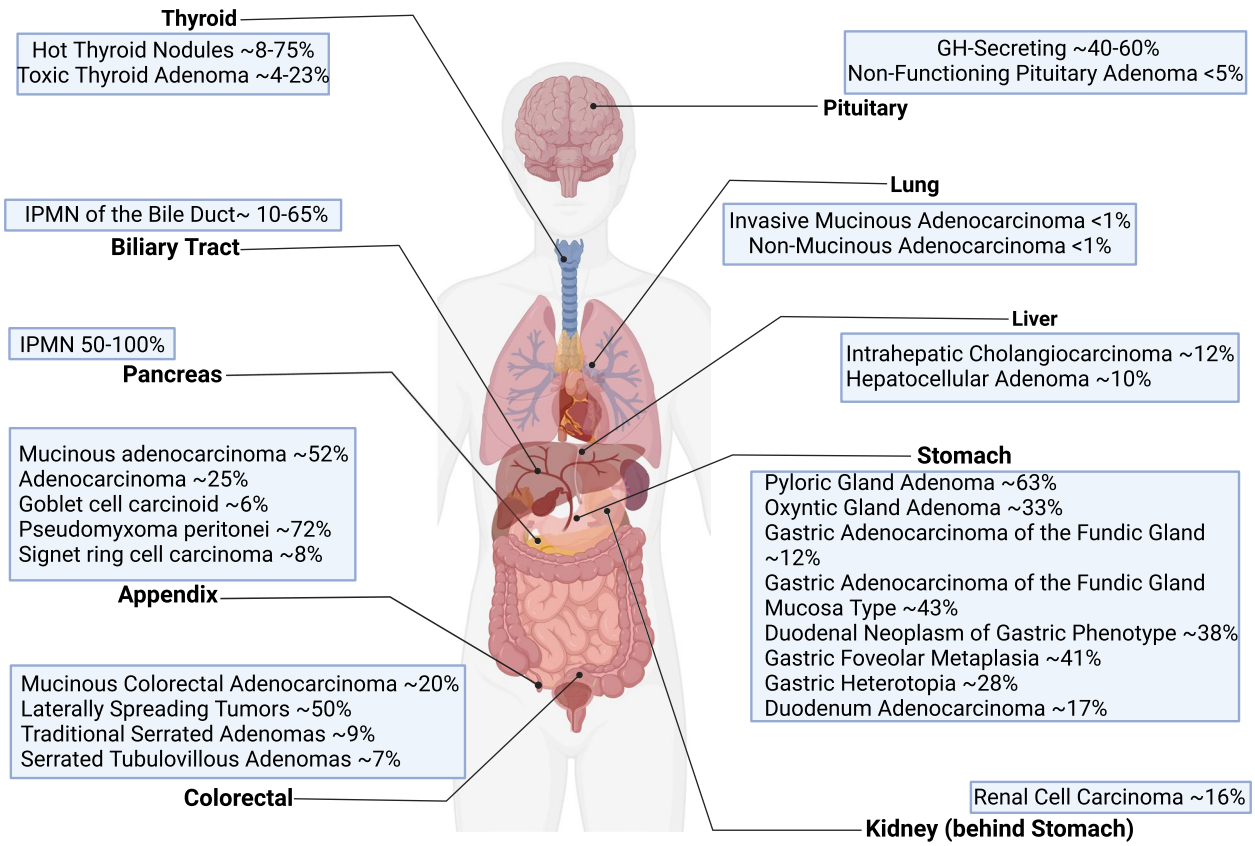

Fig. 3 *GNAS* mutation frequency in the neoplasm and cancer of various organs. All the precursor lesions and adenocarcinomas driven by GNAS activating mutations and/or have an incidence of expression with an approximate percentage of occurrence are highlighted in different organs

R201 mutation is also the most cancer-causing G protein mutation. *GNAS* mutation in different solid tumors is associated with vast mucus secretion, poor treatment response to therapy, an increase in peritoneal metastasis, and poor survival [18]. Furthermore, *GNAS* mutation either initiates the tumorigenesis as a co-driver mutation with other oncogenes or co-exists with other genetic alterations (Table 1). Here, we highlight the significance of *GNAS* mutation in neoplasms and cancers of different organs and their genomic landscape.

Brain

One of the intracranial neoplasms, a subtype of pituitary tumor known as growth hormone (GH)- secreting somatotroph adenomas, harbor 40–59.5% *GNAS* mutation [19, 20]. *GNAS* mutation-positive tumors show higher GH and insulin-like growth factor-1 levels and smaller tumor sizes than tumors negative for *GNAS* Mutation. One of the studies with a sample size reported no correlation between *GNAS* mutation and surgical remission [20]. However, another study showed a significant difference at one week and six months post-surgery [19]. While substantial in GH-secreting tumors, *GNAS* mutation is infrequent (< 5%) in other non-functioning pituitary adenomas and absent in prolactin-secreting adenoma [21]. Nonetheless, *GNAS* mutation potentially transforms aggressive prolactinoma into growth hormone-secreting adenoma. *GNAS* mutation correlation with higher dopamine receptor two expression suggests the possible significance of *GNAS* mutation in predicting the efficacy of dopamine agonist treatment in pituitary tumors [22]. *GNAS* mutation (~ 4%) is also present in a molecular subtype of medulloblastoma (MB), Sonic Hedgehog (*Shh*)- MB. Contrary to pituitary adenoma, mutant *GNAS* is reported to be tumor-suppressive in *Shh*-MB as it inhibits tumor cell proliferation and progression [23, 24]. Additionally, loss or lower expression of *GNAS* is associated with tumor aggressiveness and poor survival in *Shh*-MB [25, 26]. Hence, further investigation is warranted to understand the role of *GNAS* mutation in the molecular mechanism of *Shh*-MB for clinical significance.

Thyroid

The thyroid stimulating hormone (TSH) activates the TSH receptor (TSHR), a GPCR, and mediates the cAMP signaling axis via Gsα for the normal functioning of thyroid cells [27, 28]. Mutations in *GNAS* and TSHR result in hyperfunctioning thyroid. They are reported to give rise to hot thyroid nodules (HTN) and autonomously functioning thyroid nodules (AFTNs), which, in some cases, have a risk of malignancy [29]. Additionally, *GNAS* mutation (4–23%) is reported in toxic thyroid adenomas (TA). Thyroid carcinoma is mainly caused by the driver mutations in *BRAF* and *RAS* genes that regulate the *MAPK* signaling pathway in the thyroid cells. While there are no studies suggesting *GNAS* as the driver of oncogenic mutation for thyroid cancer, *GNAS* mutation

Table 1 Co-occurring genetic alterations of oncogenic *GNAS*

Organ/Tumor	Co-Occurring Partners
Pituitary Adenomas	*PRKAR1A, PDE4D, CDKN1B*
Thyroid Carcinomas	*TSHR, BRAF, MAPK, RAS*
Lung Adenocarcinomas	*JAK, Mucins*
IPMNs	*KRAS, RNF43, SMAD4, TP53, MUC5AC, MUC4, MUC2, CDKN2A, PIK3CA, ARID1A, LATS1, YAP1, SIKs*
Appendiceal Cancers	*KRAS, Mucin, TP53, ARID1A, SMAD4, FAT3, RNF43*
IPNB	*KRAS, RNF43, TP53, PIK3CA*
Gastric and Duodenum Neoplasms	*APC, KRAS, CTNNB1, TP53, CDKN2A, PIK3CA, EPHA5, MUC5AC*
Colorectal	*APC, TP53, FAT4, BRAF, PABPC1, MUC7, HSPG2, DENND5B, BNIP3L, Wnt/B-Catenin*
Hepatocellular Carcinoma	*SRC, STAT3*

is found in both benign and malignant thyroid [30, 31]. Like human thyroid follicular cell carcinoma (FCC), the somatic mutation in *GNAS* is also found in German long-haired pointer dogs, which can be used as a model system for further studies and therapeutic strategies [32]. *GNAS* mutation also correlates with thyroid cancer in the context of FD and MAS. There are several cases of thyroid cancer in MAS patients, as the activating mutation in *GNAS* causing FD and MAS predisposes them to cancer [33]. Over the years, four such cases have been reported in women aged 14–42 years old, suggesting that women with MAS are potentially at high risk of developing thyroid cancer.

Lung

Oncogenic *GNAS*, though rare, is associated with both mucinous and non-mucinous adenocarcinoma of the lung [34, 35]. Predominantly in females, 0.8% of lung adenocarcinomas have *GNAS* mutations with slightly higher frequency (0.53%) in invasive mucinous adenocarcinomas (IMA) than non-mucinous adenocarcinomas (0.47%) [34]. A potential correlation between smoking history in patients with *GNAS*-mutated non-mucinous adenocarcinomas is also found [36]. Further, *GNAS* and *JAK1* are identified as the driver mutation of lung adenocarcinoma in the Chinese population. In cooperation with *KRAS* mutation, *GNAS* mutation is also potentially essential for developing metastasis [37]. The significance of oncogenic *GNAS* in lung cancer investigated in the transgenic mouse model indicated that mutated *GNAS* plays a role in the initiation and progression of lung cancer [38]

Pancreas

GNAS mutation is the unique oncogenic driver of Intraductal Papillary Mucinous Neoplasm (IPMN), one of the precursor lesions of pancreatic ductal adenocarcinoma (PDAC) [39]. *GNAS* mutation is found in only ~ 2–11% of overall PDAC cases; however, ~ 40–75% of IPMN harbors *GNAS* mutation [40, 41]. The overall prevalence of *GNAS* varies in the histological subtype of IPMN, with the highest frequency in intestinal IPMN followed by gastric, pancreatobiliary, and oncocytic subtypes [42, 43]. The majority of the IPMN cases harbor both KRAS and *GNAS* mutations, and the concordant *KRAS* and *GNAS* mutations in mouse models develop cystic lesions that resemble the gastric and pancreaticobiliary subtypes of human IPMN [39, 44, 45]. In these studies, the mutant *GNAS* is well established as the oncogenic driver of IPMN tumorigenesis and metabolic reprogramming. Moreover, it is reported that mutant *GNAS* alters the *KRAS*-mediated pathway and regulates tumor aggressiveness [46]. In recent years, the IPMN-mediated PDAC, driven by *GNAS*, has become a rapidly growing field of interest. Studies have investigated the underlying mechanistic action of *GNAS* in IPMN-mediated PDAC, the potential of *GNAS* as a therapeutic target, and the biomarker [39, 42, 46, 47].

Appendix

Appendiceal cancer is a relatively rare form of cancer. It is divided into five subtypes: mucinous adenocarcinomas (Mads), adenocarcinomas (Ad), goblet cell carcinoids (GCC), pseudomyxoma peritonei (PMP), and signet ring cell carcinomas (SRCC) [48]. PMP (72%, 81%) has the highest prevalence of *GNAS* in parallel to *KRAS* mutation, followed by Mads (52%, 77%), Ad (25%, 56%), SRCC (8%, 35%), and GCC (6%, 13%) [48]. Mutations in *TP53*, *ARID1A*, *SMAD4*, and *FAT3* are more prevalent in GCC, with the lowest mutation rate in *GNAS* [48, 49]. Additionally, TP53 mutation is most common in Ad and SRCC, less so in Mads and GCC, and rare in PMP. *GNAS* mutations concurrent with mutant KRAS are associated with lower-grade tumors, while *KRAS* and *TP53* mutations correlate with higher-grade tumors [48–50]. The molecular profiles of appendiceal cancers are also distinct from colorectal cancer (CRC), with more frequent *GNAS* mutations and fewer *APC* and *TP53* mutations than CRC [48, 50, 51]. *KRAS* and *GNAS* mutations in Ad and SRCC resemble CRC profiles, and the mutation pattern in Mad and PMP mirrors that of intraductal papillary mucinous neoplasms [48]. The distinct mutational profiles from CRC and the overview of the molecular landscape of appendiceal neoplasms suggest that *GNAS* mutations can be surrogates for a histological grade of appendiceal tumors and prognosis and may guide therapeutic strategies.

Bile duct

The neoplasm of the bile duct, one of the precursor lesions of cholangiocarcinoma, is known as the Intraductal papillary neoplasm of the bile duct (IPNB) [52]. The frequent prevalence of mutations in *KRAS*, *GNAS*, *RNF43*, and *TP53* are reported [52, 53]. IPNB shares similarities with IPMN regarding a large amount of mucus production and histology, particularly the intestinal subtype driven by *GNAS* mutation [54]. Further, the intestinal subtype of IPNBs (iIPNBs) is characterized by intrahepatic iIPNBs and extrahepatic iIPNBs. The *KRAS* and *GNAS* mutations are more common in intrahepatic iIPNBs, while the extrahepatic iIPNBs show mutations in *TP53* and *PIK3CA* [54]. While very few studies have focused on IPNB tumor biology as the field is relatively new, and the number of cases examined varies is less in number, it is reported that *GNAS* mutation is found in around 10–65% of the cases examined [52–54].

Stomach

A notable association between *GNAS* mutations and gastric and duodenum neoplasms has been indicated in various studies [55–58]. Different histological subtypes of gastric and duodenal adenomas (intestinal-type, foveolar-type, pyloric gland adenomas (PGA), and gastric-type adenoma, not otherwise specified (NOS)) have distinct genetic backgrounds [58]. *GNAS* mutations are notably absent in foveolar and intestinal-type adenomas but prevalent in PGAs (63%), followed by gastric-type adenomas, NOS [58, 59]. Around 93% of gastric and duodenal PGAs with KRAS mutation have concurrent *GNAS* mutation. The mutations in the *APC*, *KRAS*, and *GNAS* genes are reported in PGAs with low-grade dysplasia, whereas, high-grade dysplasia showed mutations in genes such as *APC*, *CTNNB1*, *KRAS*, *GNAS*, *TP53*, *CDKN2A*, *PIK3CA*, and *EPHA5* [59]. In gastric adenomas, mutations in *APC* and *KRAS* correlate with the expression of certain epithelial markers, while *GNAS* mutations (13%) are significantly associated with *MUC5AC* expression. These associations are less clear in adenocarcinomas, although *GNAS* mutations remain more common in *MUC5AC*-positive lesions [60]. Various duodenal lesions such as Duodenal neoplasm of gastric phenotype (DNGP), gastric foveolar metaplasia (GFM), gastric heterotopia (GH), and adenocarcinoma of the duodenum also harbor 38%, 41%, 28%, and 17% *GNAS* mutation respectively [56, 61]. Moreover, recently comprehensive studies on the gastric epithelial neoplasm of fundic-gland mucosa lineage (GEN-FGML), one of the low-grade well-differentiated gastric tumors, proposed a new classification that emphasized the significance of *GNAS* mutation in GEN-FGML [62, 63]. The three major subtypes of GEN-FGML, oxyntic gland adenoma (OGA), GA-FG, and gastric adenocarcinoma of fundic-gland mucosa type (GA-FGM) exhibited 33.3%, 12.5%, and 42.9% *GNAS* mutation respectively [62–64]. Another study reported *GNAS* mutation in 19.2% of GAFGs [65]. Overall, these studies have highlighted the occurrence of *GNAS* mutations in rare gastric and duodenal neoplasms with gastric phenotypes, further emphasizing the role of *GNAS*, particularly in those with gastric epithelial differentiation. These indicate the importance of genetic profiling in evaluating gastric tumors, aiding in understanding their pathogenesis and potentially guiding therapeutic approaches.

Colon and rectum

Only 5% of CRC patients, particularly mucinous colorectal adenocarcinoma (20%), harbor *GNAS* mutation; however, the oncogenic Gsα plays a vital role in the prognosis and treatment of CRC [66, 67]. Primary CRCs have higher *GNAS* mutations compared to peritoneal metastases [68]. A new *GNAS* mutation, R186C/H (50%) has been identified in CRC Laterally spreading tumors (LST), with significant occurrence in the rectum compared to the colon [69]. Additionally, this mutation showed a significant correlation with histological type, which is more prevalent in villous adenoma than tubular adenoma. *GNAS* mutations are reported in 9.2% of traditional serrated adenomas and 7.1% of serrated tubulovillous adenomas [70]. Further, unlike rectal adenocarcinoma, *GNAS* mutation is not found in rectal squamous cell carcinoma [71]. *GNAS* mutation, among many other frequently altered genes in CRC, in part, is significant in different molecular profiles of CRC patients based on the geolocation [72]. CRC cases in Europe reported alterations in *APC, TP53, FAT4,* and *BRAF* genes, whereas the Korean CRC (KOCRC) showed *PABPC1, MUC7, HSPG 2, GNAS*, and *DENND5B.* Further, another study based on the meta-analyses of seven Genome-wide association studies on East Asian CRC patients also impresses upon the mutation in *GNAS* and *DENND5B*, consistent with the KOCRC genomic landscape [73].

Other organs

The oncogenic effect of *GNAS* mutation has also been associated with organs such as the liver and kidney. The role of *GNAS* mutation in kidney and liver tumorigenesis is debatable, as there are not enough studies to draw specific conclusions. *GNAS* mutation was found in around 12% of Intrahepatic cholangiocarcinoma patients, significantly decreasing in Intrahepatic cholangiocarcinoma with chronic advanced liver disease [74]. A subset of Hepatocellular carcinoma (HCC) patients also reported the point mutation in *GNAS*, resulting in tumor development, progression, and poor survival [75, 76]. Moreover, *GNAS* mutation is reported in around 16% of kidney cancers [77]. Further, *GNAS* is detected in the circulating tumor DNA from the blood and urine samples of metastatic renal cell carcinoma [78].

Mechanistic action of gsp: aftermaths of an incessant active state

The gsp oncogene mainly exploits the canonical *GNAS*/Gsα – cAMP signaling pathways. It asserts a profound impact on tumor progression and maintenance due to the continuous activation of cAMP-PKA downstream signal transduction (Fig. 4). $GNAS^{R201C}$ – cAMP—*PKA* activates the Hippo Kinase pathway in IPMN-PDAC, leading to the phosphorylation of *LATS1* and *YAP1* [45]. This results in the cytoplasmic sequestration of *YAP1* and the development of well-differentiated tumors. Pancreatic *KRAS*; *GNAS* mouse model and derivatives demonstrated that $GNAS^{R201C}$ alters the genetic phenotype of pre-invasive lesions and progresses to predominantly well-differentiated invasive carcinoma via repression of

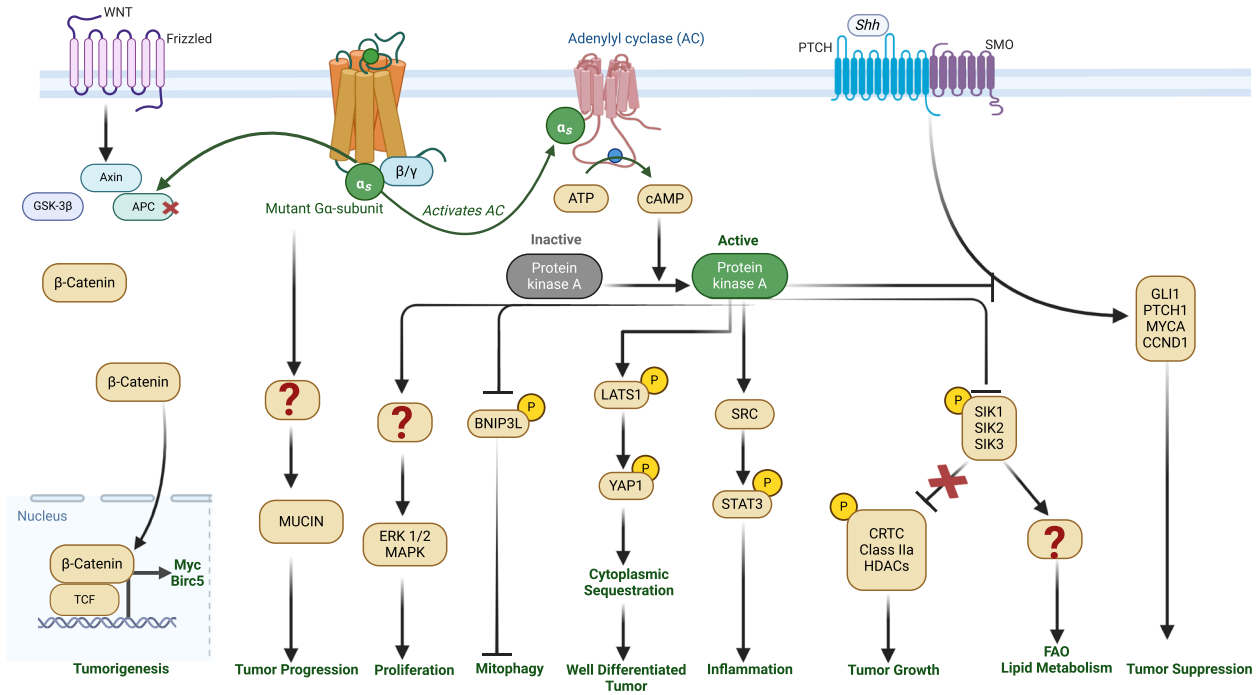

Fig. 4 Oncogenic *GNAS* activation and downstream signal transduction**.** The Gsp oncogene drives tumor progression through persistent activation of cAMP-PKA signaling. It activates the Hippo pathway, leading to tumor differentiation, promotes lipid metabolism via salt-inducible kinases (SIKs), and enhances tumor growth. It drives proliferation via the PKA-ERK1/2-MAPK axis and inflammation by activating the PKA-SRC-STAT3 pathway. It promotes tumorigenesis by inhibiting mitophagy and activating Wnt/β-catenin signaling. *GNAS* also acts as a tumor suppressor by negatively regulating the Shh signaling pathway. These pathways underscore the diverse roles of *GNAS* mutations in cancer progression

YAP1 and its target genes [45]. Further, $GNAS^{R201C}$ targets the salt-inducible kinases and promotes fatty acid oxidation and lipid metabolism reprogramming via lipid synthesis, hydrolysis, and remodeling in IPMN-PDAC [39]. The activation of the downstream molecules of *SIK*, such as *CRTC2-S171*, *CRTC2-S275*, and *HDAC7-S155*, also promotes tumor growth.

Recent studies have exhibited the involvement of gsp in the inflammatory-mediated progression of Hepatocellular carcinoma (HCC) [75, 79]. While in the HCC with mutant gp130, inflammation is activated via *IL6-JAK-STAT3* signaling, the inflammatory response is triggered via the *PKA-SRC-STAT3* pathway in the HCC with gsp oncogene [79]. Another study suggests that gsp releases the inhibitory function of long non-coding RNA, *TPTEP1*, on *STAT3*, resulting in inflammation-induced HCC progression [75]. In intestinal cancer, the gsp oncogene enhances tumor proliferation due to the activation of the canonical *PKA- ERK1/2- MAPK* axis [80]. In contrast to IPMN and HCC, where *GNAS* mutation induces an increase in cell proliferation, the activation of $GNAS^{R201C}$-cAMP-*PKA* suppresses the cell proliferation and overexpression of cAMP-hydrolyzing phosphodiesterase 4D (PDE4D) in CRC [81]. However, *in cooperation with the GPR176 receptor, GNAS* activates another cAMP-PKA-mediated downstream signaling, inhibits mitophagy via the phosphorylation of *BNIP3L*, and promotes tumorigenesis and progression of CRC [82].

In addition to the oncogenic effects through the conventional downstream transductions of cAMP-*PKA*, *GNAS* mutation influences other signaling pathways to maintain its dominance in tumors (Fig. 4). The cooperation of gsp with the loss of *APC* in intestinal tumors impedes the binding of *GSK-3β* and *APC*/Axin complex and reduces the degradation of *β-catenin* [17, 80]. Henceforth, the increase in the expression of Wnt target genes such as *MYC* and *Birc5* via the activation of the transcription factor *TCF4* drives colorectal tumorigenesis. While the underlying mechanism is still unclear, the *Wnt/β-catenin* signaling pathway is activated by gsp in a subset of Gastric adenocarcinoma of the fundic gland type (GAFG) and colorectal tumors [17, 65]. The notable correlation between oncogenic *GNAS* mutation and vast mucus production in various neoplasms, such as IPMN and gastric, is highlighted in many studies [45, 60]. However, further studies are important to elucidate the underlying mechanism.

Targeting *GNAS*: beginning of a new era

GTPases, such as *KRAS* and G proteins, have been infamous for their "undruggable" status for decades due to their intracellular location, high affinity for guanine nucleotide, and lack of accessible drug binding sites [83, 84]. The identification of cyclic peptide inhibitor for $KRAS^{G12D}$ – effector interaction, cyclic peptide ligands of $KRAS^{G12D}$ selective to GTP-state, $KRAS^{G12C}$ inhibitor, Adagrasib (MRTX849), which targets the mutant cysteine in GDP-bound state and *KRAS*-dependent pathways have promoted *KRAS* to the druggable status [85–88]. Inspired by these drastic advancements in the field, the focus has been on targeting the gsp oncogene in the last few years (Fig. 5).

Direct inhibition of Gαs/Gsp

The selective inhibitors like FR900359 and YM-254890 for α subunits of heterotrimeric G proteins such as Gq and 11 demonstrated promising results in targeting mutant G proteins [89, 90]. However, the lack of flexibility for derivatization has hindered utilizing this as a scaffold in developing new cyclic peptide inhibitors for other mutant G proteins. Moreover, a recent discovery that mutation can activate GDP-bound Gαs without GTP binding by stabilizing the intramolecular hydrogen bond network has unlocked the potential to exploit both GDP and GTP states of gsp oncogene [84]. Recently, a comprehensive platform, the Random nonstandard Peptide Integrated Discovery (RaPID) system, was used to identify cyclic peptides that selectively target specific Gαs protein conformations, both GTP and GDP state [91]. Two macrocyclic peptides, GN13 and GD20, that can bind to the active and inactive state of Gαs, respectively, were identified [91]. The strong binding of these peptides to Gαs and their flexibility for further modulation, as displayed by their analogs, cpGN13 and cpGD20, to attain better stability and cell permeability properties paves a path for the development of inhibitors for G proteins and other GTPases. The high affinity of these peptides for nucleotide-state selectivity, G protein class specificity, as indicated by little to no binding to Gα13, Gαq, and Gαi, and their ability to target all the oncogenic mutants of Gαs challenges the current status of targeting oncogenic *GNAS* [91].

For the first time, a study targeting *GNAS* mutation in PMP presented Gsα as an ideal neoantigen candidate for vaccine therapy [92]. T cells from PMP patients stimulated with synthetic mutant Gsα peptides demonstrated strong immunogenicity of peptides and further indicated the possibility of an innate immunological response to

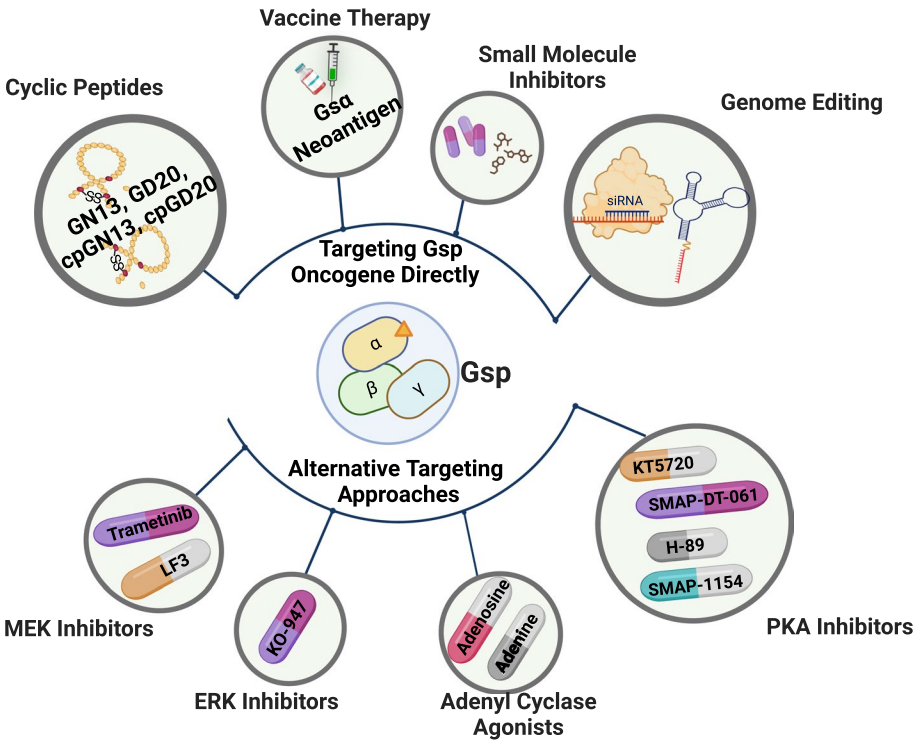

Fig. 5 Strategies for targeting the *GNAS* mutation-driven tumors. Cyclic peptide inhibitors such as GN13 and GD20, vaccine therapy, inhibitors of downstream molecules regulated by *GNAS* such as H-89, Trametinib, LF3, etc., and various genome editing tools like CRISPR-Cas9 and antisense oligonucleotides (ASOs) offer promising therapeutic options for GNAS-driven cancers

altered Gsα. Infiltrating the T cell population (CD4 + and CD8 +) with the significant expression of *PD-1* and *TIGIT* in the immune microenvironment suggested that these T cells are antigen-exposed in PMP. This study explored the possibility of vaccinating with Gsα mutant peptides in combination with immune checkpoint inhibitors as a novel treatment for PMP. While the sample cohort in the study was small and the study lacks clinical proof as all the findings are pre-clinical model-based, this primary study shows that targeting mutated Gsα with the vaccine could be a promising approach not just in PMP but also other diseases, driven by mutated Gsα. Further investigation, like a clinical trial, as mentioned in the study, using this peptide in PMP and other Gsα –driven diseases is vital to acquire clinical evidence for using vaccine therapy against gsp oncogene.

Targeting upstream receptors, downstream effectors, and signaling pathways

Repurposing drugs to target the downstream molecules and pathways mediated by the gsp oncogene has also demonstrated anti-tumor properties. The oncogenic addiction of *GNAS* mutation is mediated mainly by its downstream effectors, cAMP and *PKA* [39, 45, 79]. While there are no drugs for directly targeting cAMP, the inhibition of AC with P-site inhibitors such as adenosine and adenine nucleotide analogs and AC inhibitors show potential in affecting cAMP levels [93]. Targeting PKA by a pharmacological inhibitor, H-89, significantly reduced the growth of CRC organoids harboring *GNAS* mutation [17]. The suppression of *PKA* phosphorylation by two small-molecule activators, SMAP-1154 and SMAP-DT-061, reduced tumor growth in SCLC xenografts [38]. The combination treatment of chemotherapy, cisplatin, and SMAP-DT-061 also induced apoptosis in SCLC. Another *PKA* inhibitor, KT5720, significantly hindered the growth of *GNAS*-mutant IPMN-mediated PDAC organoids [39]. The inhibition of the *ERK1/2 MAPK* pathway with various *MEK*, *ERK*, and *MAPK* inhibitors has been reported to halt the tumor and disease progression in tumors driven by Gαs mutations [80, 94, 95]. *MEK* inhibitor, Trametinib treatment administered in the NSCLC, PDAC, Mad, and PMP tumor patients harboring oncogenic *GNAS* mutations showed improvement in the symptoms and delay in tumor progression [94–96]. The disruption in the interaction between β-catenin and its ligand with a small molecule inhibitor, LF3, has also slowed the growth of CRC-derived organoids harboring *GNAS* mutation [17]. Additionally, Gαs mediated signaling pathways are activated in response to the stimulation of GPCRs by agonists, reducing the activity of GPCRs that signal through Gαs can alleviate the continuous signal transduction. Around 35% of currently FDA-approved drugs target GPCRs, including Ga protein subtypes. Drugs and antagonists specific to GPCRs with which Gαs protein associate could also be therapeutically beneficial in oncogenic Gαs-driven neoplasms and cancers.

Genome editing

The potential of gene editing technologies to precisely target and correct mutations in oncogenes shows very promising potential in targeting the oncogenes [97]. Studies have reported that the inhibition of *GNAS* by a genetic alteration in vitro using cell lines and organoids has delayed tumor growth and progression and increased the anti-tumor immune response [17, 75, 82, 98]. Hence, the inhibition and correction of activating mutation in *GNAS* using CRISPR-Cas9, siRNAs could be explored as a therapeutic approach to mitigate the effects of mutant *GNAS* in many cancers. Additionally, antisense oligonucleotides (ASOs) are chemically modified DNA-like molecules designed to complement specific RNA sequences and represent a promising therapeutic approach for targeting mutated genes, such as cancer-related genes, among others [99, 100]. ASOs have been reported to specifically inhibit the expression of many different genes and delay tumor progression in many preclinical models of cancers and other diseases [101–103]. These technologies are still in the research and experimental stages for many cancers and include many challenges, such as delivery methods and off-target effects. However, these approaches could potentially fix the mutations in *GNAS* and restore normal function by precisely targeting and altering specific DNA sequences.

Conclusion

GNAS mutations play a significant role in developing and progressing various tumors and neoplasms, particularly through their impact on signaling pathways that regulate cell growth and differentiation. These mutations contribute to aberrant activation of the downstream signaling cascades and are implicated in tumorigenesis and disorders, which are at risk of developing cancer. The in-depth understanding of the significance of oncogenic *GNAS* and the mechanisms by which these mutations drive tumorigenesis sheds light on the biological underpinnings of neoplasms and tumors. Further, the molecular and genomic landscape of *GNAS*-driven cancers and the association between the oncogenic mutation and molecular pathways could open avenues for therapies to mitigate the effects of *GNAS* mutations. While targeting mutant *GNAS*/Gαs remains a significant challenge, with the continuous efforts and ongoing research to explore innovative

drugs and therapies, more effective treatments will likely emerge, improving outcomes for patients with *GNAS* mutations. The multi-faceted approach, combining direct inhibition, upstream receptors, and downstream effector targeting, genetic therapies, and personalized medicine, might be essential in overcoming the oncogenic consequence of *GNAS* mutations.

Abbreviations

GNAS	Guanine Nucleotide Alpha-Stimulating Binding Protein
Gsα	Gs-A Long
GNAS A/B	Gs-A Short
XLαs	Extra-Long A S
ALEX	Alternative Gene Product Encoded by XL Exon
PHP	Pseudohypoparathyroidism
PPHP	Pseudopseudohypoparathyroidism
AHO	Albright Hereditary Osteodystrophy
POH	Progressive Osseous Heteroplasia
OC	Osteoma Cutis
FD	Fibrosis Dysplasia
MAS	Mccune-Albright Syndrome
R201	Arginine 201
Q227	Glutamine 227
GH	Growth Hormone
MB	Medulloblastoma
SHH	Sonic Hedgehog
TSH	Thyroid Stimulating Hormone
TSHR	Thyroid Stimulating Hormone RECEPTOR
HTN	Hot Thyroid Nodules
AFTN	Autonomously Functioning Thyroid Nodules
FCC	Follicular Cell Carcinoma
IMA	Invasive Mucinous Adenocarcinomas
IPMN	Intraductal Papillary Mucinous Neoplasm
PDAC	Pancreatic Ductal Adenocarcinoma
Mad	Mucinous Adenocarcinoma
Ad	Adenocarcinomas
GCC	Goblet Cell Carcinoid
PMP	Pseudomyxoma Peritonei
SRCC	Signet Ring Cell Carcinomas
CRC	Colorectal Cancer
IPNB	Intraductal Papillary Neoplasm of The Bile Duct
iIPNB	Intestinal Intraductal Papillary Neoplasm of The Bile Duct
PGA	Pyloric Gland Adenoma
NOS	Not Otherwise Specified
OGA	Oxyntic Gland Adenoma
GAFG	Gastric Adenocarcinoma of The Fundic Gland Type
DNGP	Duodenal Neoplasm of Gastric Phenotype
GFM	Gastric Foveolar Metaplasia
GH	Gastric Heterotopia
GEN-FGML	Gastric Epithelial Neoplasm of Fundic-Gland Mucosa Lineage
LST	Laterally Spreading Tumor
KOCRC	Korean Colorectal Cancer
HCC	Hepatocellular Carcinoma
ASO	Antisense Oligonucleotide

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Authors' contributions
P.R: Conceptualization, designed outline, drafted the contents, designed figures, and wrote and proofread the manuscript; P.M: drafted the contents and proofread the manuscript draft; S.K.B and M.P.P: Critical review, important intellectual inputs, final approval of content and correspondence; All authors read and approved the manuscript's content before final submission.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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