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VGF and Its Receptors in Human Cancers: Molecular Mechanisms, Oncogenic Functions and Clinical Perspectives

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ABSTRACT
VGF (nerve growth factor-inducible; also secretogranin VII/SCG7/SgVII) is a secreted neuroendocrine polyprotein that is induced by nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and other stress and injury signals, then processed by prohormone convertases into multiple bioactive peptides, including TLQP-21, TLQP-62, NERP-1/2, and others. Although historically studied for energy homeostasis, pain, depression, and neurodegeneration, VGF is increasingly implicated in human malignancies. Functionally, VGF acts through a family of peptide fragments rather than a single VGF receptor: its activity is mediated predominantly by peptide fragments engaging distinct receptors and binding partners - best characterized being TLQP-21 acting on C3AR1-positive myeloid cells, with C1QBP /gC1qR and HSPA8 as candidates, TrkB for TLQP-62, and TGFBR2 in uveal melanoma. Notably, the cellular expression of TLQP-21 receptors is sharply divergent, as C3AR1 is restricted to the myeloid compartment (macrophages) and is undetectable in all malignant epithelial populations, whereas C1QBP is ubiquitously expressed across tumor, stromal, and immune cells. In cancer, VGF expression is upregulated in many lineages and associates with neuroendocrine differentiation, EGFR-TKI resistance, epithelial-mesenchymal transition (EMT), chemoresistance, brain and liver metastatic niche formation, macrophage polarization, and immune infiltration. This review synthesizes VGF molecular biology, its receptor/binding landscape, tumor-specific evidence, prognostic value, and therapeutic strategies including anti-VGF antibodies, TLQP mimetics/antagonists, receptor modulation, and combination targeting with TGF-β/MAPK/PI3K pathways.

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1. Introduction

The identification of VGF dates to studies of PC12 pheochromocytoma cells, in which NGF rapidly induced a delayed-early transcript encoding a proline-rich secretory protein [1, 2]. Human VGF maps to chromosome 7q22.1, produces a ~615-amino-acid precursor (rodent ~617), and is classified within the extended granin/secretogranin family because of its residence in dense-core secretory vesicles, paired basic cleavage motifs, and neuroendocrine distribution [3, 4]. VGF mRNA is abundant in brain (especially hypothalamus, hippocampus, cortex, brainstem) and in pituitary, adrenal medulla, pancreatic islets, gastrointestinal neuroendocrine cells, and some gonadal tissues [4, 5]. Under stimulatory conditions, it is packaged in secretory granules and cleaved by prohormone convertases PCSK1/PC1 and PCSK2/PC2 into a tissue-specific peptide mixture [3, 6].

In oncology, three features make VGF interesting. First, it is a genuine neuroendocrine marker; tumors with neuroendocrine differentiation (small-cell lung cancer [SCLC], large-cell neuroendocrine carcinoma [LCNEC], some pituitary/pancreatic/gastroenteropancreatic neuroendocrine neoplasms, and treatment-induced neuroendocrine transdifferentiation in lung and prostate adenocarcinoma) often show high VGF [7-9]. Second, VGF is secreted, so it can remodel the tumor microenvironment (TME)

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via paracrine loops-blood-brain barrier disruption, microglial activation, macrophage polarization, stellate-cell fibrogenesis, and stromal reciprocal signaling [8, 10, 11]. Third, individual VGF peptides may have opposing net effects: the precursor/full-length secretory output often correlates with proliferation, resistance, and metastasis, whereas defined fragments such as TLQP-21 can suppress tumor-associated macrophages in pancreatic models [11]. This duality complicates biomarker interpretation but opens multiple therapeutic angles.

A terminology caveat is necessary because "VGF" is easily confused with "VEGF." VEGF/VEGFR refers to vascular endothelial growth factor receptors and anti-angiogenic therapeutics [12, 13]; VGF is unrelated biologically except insofar as VGF-dependent inflammation or stromal signals indirectly affect angiogenesis [14]. This review uses "VGF" exclusively for nerve growth factor-inducible protein.

2. Molecular biology of VGF

2.1 Gene regulation and induction

The VGF promoter contains SP1, AP2, CREB/cAMP-response, and NGF-responsive elements [1, 4]. In neuronal models, NGF and BDNF induce VGF through Ras/MAPK and CREB; synaptic activity, seizures, salt loading, fasting, and circadian cues modulate hypothalamic expression [4, 15]. In cancer, CREB is a recurrent upstream driver: EGFR-TKI-resistant lung adenocarcinoma and Gαq-mutant uveal melanoma both show CREB-dependent VGF transcription [8], and prostate bioinformatics implicate CREB1 together with SP1, MAZ, and NR3C1 [9]. HDAC1 binding at the VGF locus can silence or, under inhibitor exposure, derepress VGF in lung models, explaining epigenetic plasticity during neuroendocrine transdifferentiation [7]. Hypoxia can induce VGF in prostate models via migration/invasion programs [9], linking it to HIF and PI3K/Akt axes common in solid tumors.

2.2 Protein processing and peptide repertoire

VGF is synthesized as a precursor, traffics through Golgi/vesicular compartments, and undergoes cell-type-specific cleavage at basic residues [3, 14]. Major products include:

a. TLQP-21: C-terminal 21-mer, the best-characterized VGF peptide; regulates lipolysis, energy expenditure, nociception, stress, gastric function, and immune cell signaling [16-19].
b. TLQP-62: longer C-terminal fragment implicated in memory, depression-like behavior, and TrkB/CREB activation; also reported to modulate insulin secretion [20-24](PMID: 25917832).
c. NERP-1 and NERP-2 (neuroendocrine regulatory peptides): modulate vasopressin release and hypothalamic fluid/feeding homeostasis via GABAergic and glutamatergic interactions [25].
d. AQEE-30/other mid-molecules and antimicrobial C-terminal stretches: less studied in cancer but relevant to infection/inflammation interplay [26].
e. Full-length/partial VGF and granin-like fragments: may act as scaffolding/secretory factors and, in some contexts, directly bind partner proteins rather than activating a single receptor [27].

Because processing varies by cell type and convertase expression, a tumor may score "VGF-high" by RNA or immunohistochemistry yet produce different peptide mixtures than neural tissue. This explains partly why bulk VGF and individual peptides have different associations with outcome [24, 28, 29].

2.3 Secretion and spatial distribution

Human Protein Atlas and UniProt classify VGF as secreted, with vesicular/Golgi residence and brain/pituitary enrichment; HPA flags unfavorable association in glioma, lung adenocarcinoma, and prostate cancer, and a favorable association in pancreatic cancer [30]. Secreted VGF peptides can act at a distance (adipose lipolysis via sympathetic TLQP-21) or locally (hypothalamic neurons, tumor–stroma contacts) [16]. In cancer, secreted VGF from organotropic cells conditions pre-metastatic niches: breast brain-metastatic clones disrupt BBB and activate microglia [31]; uveal melanoma cells activate hepatic stellate cells [10]; pancreatic models alter macrophage complement signaling [11].

3. Receptor and binding-partner landscape

A central issue for translational work is that VGF does not signal through one receptor, but different VGF fragments engage different proteins [16].

3.1 C3AR1 as TLQP-21 receptor

TLQP-21 is intrinsically disordered in solution and adopts an α-helical conformation upon binding C3AR1, the complement C3a receptor and a family A GPCR [32, 33]. C3AR1 antagonism competes with TLQP-21; C-terminal residues (the conserved Arg21 and the species-divergent position 20: Ser in

human, Ala in rodent) are hot spots, and the binding mode overlaps but is not identical to C3a anaphylatoxin [16]. A critical review and subsequent medicinal chemistry work concluded that among proposed TLQP-21 targets-C3AR1, gC1qR/C1QBP, and HSPA8-only C3AR1 has necessary and sufficient evidence for receptor function in most assays [16, 34]. In pancreatic cancer, TLQP-21 suppression of tumor-associated macrophages was linked mechanistically to C3AR1 and C1QBP, with improved gemcitabine response and reduced allodynia/cachexia in orthotopic mice [11]. Thus, C3AR1 is both a metabolic/immune GPCR and a likely mediator of TLQP peptide effects in tumors carrying C3AR1-positive myeloid cells [16].

3.2 C1QBP and complement-related modulation

The C1QBP (p32/gC1qR/HABP1) protein was proposed as a TLQP-21 binding protein in macrophages/microglia with calcium-dependent effects and nociceptive hypersensitivity [35]. In PDAC, C1QBP together with C3AR1 contributed to M2-macrophage suppression by TLQP-21 [11]. The evidence is strongest for binding/modulation rather than classical G-protein coupling; in therapeutic models it may represent a co-factor or accessory interaction that shapes myeloid response [16].

3.3 HSPA8 and cell-surface chaperone interactions

Affinity purification from SH-SY5Y neuroblastoma identified HSPA8 (Hsc70) as a surface-binding partner for human TLQP-21, supported by cross-linking, dynamic mass redistribution, and docking [16, 36]. HSPA8 is plausible for cell-surface chaperone/scavenger receptor-like presentations but lacks a confirmed signal-transduction cascade as a sole receptor [37]. In cancer, HSPA8 involvement is hypothesis-generating for neuroblastoma, glioma, or stressed tumor cells, but should not be presented as a validated oncogenic receptor [38].

3.4 TrkB/NTRK2 for TLQP-62 and neurotrophin crosstalk

TLQP-62 can induce acute TrkB phosphorylation and CREB activation, linking VGF peptides to BDNF-like synaptic and memory pathways [39]. In tumors with NTRK fusions or TrkB-dependent survival (e.g., certain neuroendocrine, thyroid, lung, CNS tumors), TLQP-62/TrkB crosstalk could modulate proliferation or differentiation, though direct cancer evidence remains limited [40]. More broadly, NGF/BDNF upregulate VGF, whose TLQP-62 product in turn engages TrkB, creating a feed-forward neuroendocrine loop worth testing in neuronally differentiated cancers [40].

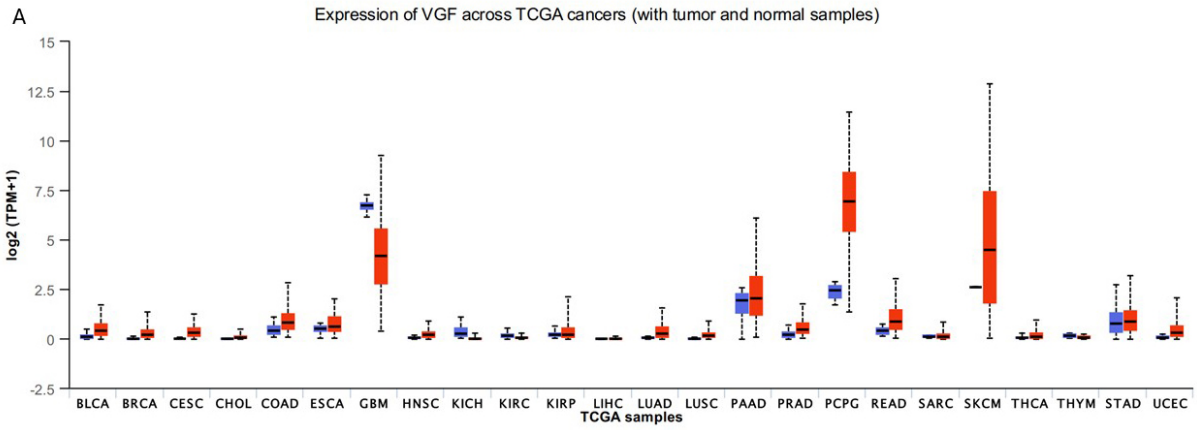
3.5 Non-peptide protein partners: TGFBR2, integrins, and stromal receptors

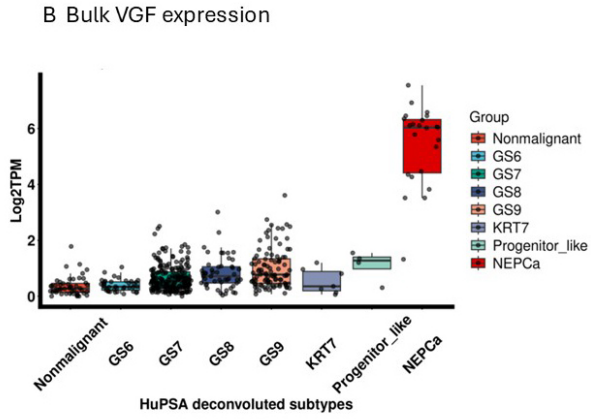
Full-length VGF or secreted fragments can bind proteins that are not GPCRs. In Gαq-mutant uveal melanoma, VGF directly interacts with TGFBR2, activates TGF-β/SMAD, promotes endothelial-mesenchymal transition-like genes, and via paracrine loops activates hepatic stellate cells to foster liver colonization [10]. In NSCLC, integrin αVβ1 signaling through PYK2 and STAT3 upregulates VGF, positioning VGF downstream of adhesion/cytokine signaling rather than as a receptor[41]. These examples show that "VGF receptors" in cancer include indirect sensor proteins: TGFBR2 as an effector partner, complement receptors for peptides, TrkB for memory-related fragments, and integrin/STAT3 pathways as upstream regulators. Any therapeutic roadmap must specify which VGF fragment and which binding partner is targeted.

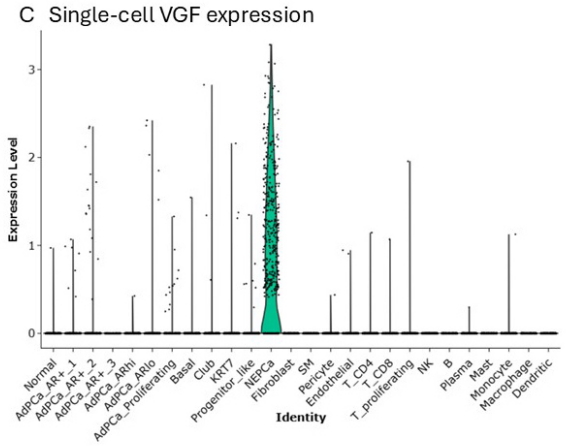
3.6 Why receptor ambiguity matters clinically

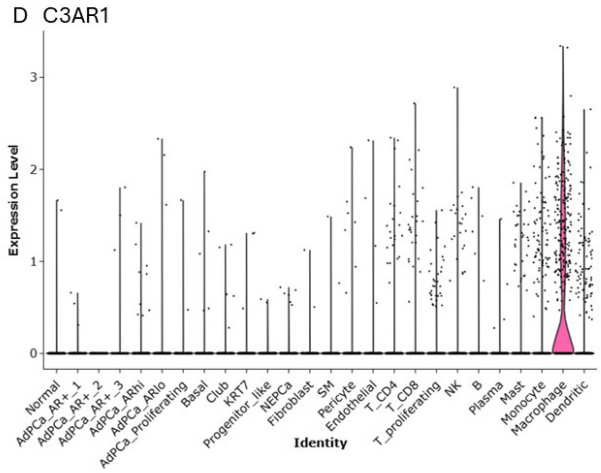
Receptor ambiguity is not a taxonomic nuisance; it has direct clinical consequences. An assay measuring total VGF RNA or protein integrates the precursor and all derived peptides while ignoring convertase state and therefore cannot distinguish protumor full-length VGF from antitumor TLQP-21. A TLQP-21 therapy acts only where its receptor is, in the myeloid compartment defined by C3AR1/C1QBP abundance. A therapy blocking the secreted full-length VGF–TGFBR2 interaction will, in effect, partially reproduce TGF-β pathway inhibition, with its attendant toxicities. Receptor mapping must therefore be matched to fragment, tumor histology, and stromal composition. Critically, receptor identity is only half of the story-receptor expression topology determines what a TLQP-21 strategy can and cannot achieve. For example, single-cell profiling of prostate tumors offers a clear example: C3AR1 was confined to the myeloid compartment and undetectable in every malignant epithelial population, including NEPC, whereas C1QBP was broadly expressed across tumor, stromal, and immune cells (Fig. 1D, E). The general lesson is that TLQP-21 should be regarded as a myeloid-reprogramming signal rather than a tumor-cell-directed ligand, and that C1QBP co-expression on tumor cells should not be mistaken for tumor-cell-autonomous receptor function.

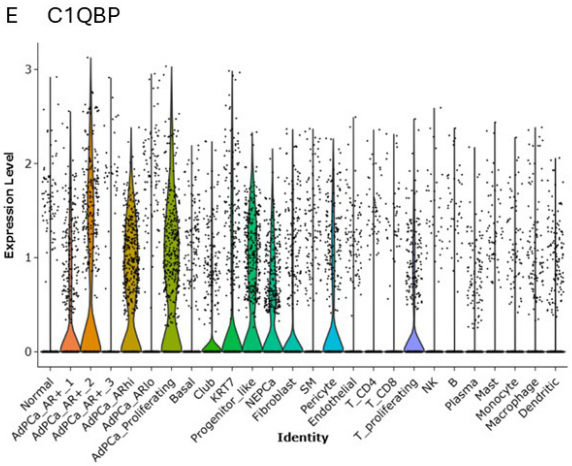
Fig. 1A. Pan-Cancer view of VGF gene expression in various cancers (red bar) compared to normal tissue compartments (blue bar) with the TCGA RNA-seq datasets generated on the UALCAN web platform [58].
Fig. 1B-1E. Bulk-cell (panel **B**) and single-cell (panel **C-E**) sequencing data for VGF (C) , C3AR1 (D) and C1QBP (E) gene expression in different types of prostate cancer cells were analyzed and visualized on the HuPSA/MoPSA web platform as reported previously [52].











4. Pan-cancer expression patterns and general prognostic signals

Pan-cancer bioinformatics using TCGA/GTEx/TIMER consistently reports VGF mRNA elevated in most tumor types relative to normal tissues, with variable magnitude (Fig 1A) [42, 43]. In an ACC dataset, VGF was higher in tumor versus normal adrenal, associated with stage, nodal involvement, metastasis, and poor overall survival; pathway analysis implicated cytokine-receptor interaction and PI3K-Akt [42]. In head/neck squamous cell carcinoma (HNSCC) and oral squamous cell carcinoma (OSCC), TIMER-based pan-malignant analysis and local cohorts showed VGF upregulation, advanced stage/node positivity, and worse survival; a regulatory axis linking miR-432-5p, VGF, and IL23R was proposed [43]. Human Protein Atlas lists unfavorable VGF in glioma and endometrial cancer [30]. These data support VGF as a broadly pro-tumor transcriptional signature but with exceptions: PDAC bulk high VGF can be associated with poor biology overall, yet TLQP-21 administration is beneficial [11], indicating fragment-specific effects.

5. Tumor-type evidence

5.1 Lung: SCLC, LCNEC, EGFR-TKI resistance, and NSCLC

High-grade lung neuroendocrine tumors express VGF strongly [7]. In SCLC and LCNEC, VGF promotes growth and chemoresistance; silencing induces BMF and BCL2L11, sensitizing cells to chemotherapy [7]. In EGFR-mutant adenocarcinoma, acquisition of resistance to gefitinib/erlotinib/ afatinib selects VGF-high subpopulations; VGF overexpression induces TWIST1, EMT, migration, and TKI insensitivity, while silencing resensitizes cells and suppresses xenograft growth [8]. HDAC1 occupies the VGF locus, and HDAC inhibitor exposure can paradoxically increase VGF, underscoring epigenetic context [7, 44]. In broader NSCLC, integrin αVβ1 activation through PYK2 and STAT3 induces VGF and promotes progression, providing a non-neuroendocrine adhesive-signal entry point [41]. Clinically, VGF in lung adenocarcinoma correlates with advanced grade and poor survival, and in SCLC it tracks with high-grade neuroendocrine phenotype and resistance [7, 8]. These findings support VGF as a neuroendocrine/resistance marker and a candidate target in TKI-relapsed or histologically transformed disease. Secretome analysis originally identified VGF peptides in the conditioned medium of pulmonary large cell neuroendocrine carcinoma (LCNEC) cells, nominating VGF as a candidate serological marker for LCNEC [63].

Beyond chemoresistance, VGF has recently been implicated in the lineage plasticity of SCLC itself. In ASCL1$^+$ SCLC, Ding et al. identified secreted VGF as a critical regulator of neuroendocrine differentiation: VGF upregulated the lineage-defining transcription factor ASCL1 through a CREB-dependent mechanism, while concomitantly driving the transformation of fibroblasts into cancer-associated fibroblasts (CAFs) and establishing lactate-mediated metabolic coupling between SCLC cells and CAFs [59]. Notably, dual targeting of VGF and monocarboxylate transporter 1 (MCT1) disrupted both neuroendocrine differentiation and SCLC-CAF metabolic coupling, showing significant efficacy *in vitro* and *in vivo [59].* This study positions VGF at the intersection of neuroendocrine identity and stromal metabolic symbiosis and provides a rationale for combining anti-VGF with metabolic inhibitors in SCLC.

5.2 Breast cancer and brain metastasis

Brain metastasis is a major breast cancer problem with limited targeted options [45]. Secretome comparisons of brain-organotropic versus non-organotropic cells identified VGF as a mediator of BBB disruption and microglial activation in vitro and in vivo [31]. In human breast cohorts, VGF expression in tumor cells and adjacent stroma was associated with worse prognosis, HER2 and triple-negative subtypes, and specifically with brain metastatic location [31]. Mechanistically, VGF conditioned medium increased permeability-related endothelial changes and microglial inflammatory phenotype, creating a pre-metastatic niche [46]. For biomarker use, VGF IHC or secreted VGF/peptide profiling could enrich for brain-metastasis risk in HER2$^+$ and TNBC [42, 47]; therapeutically, anti-VGF or peptide-receptor modulation could be tested alongside CNS-penetrant agents and immunotherapy, noting that immunotherapy delivery across the BBB remains a constraint. In support of a myeloid mechanism, the VGF-derived peptide TLQP-21 has been shown to modulate microglial function through C3AR1 signaling [67], consistent with the microglial inflammatory phenotype observed in the brain-metastasis niche.

5.3 Uveal melanoma and liver colonization

Uveal melanoma (UM) is the most common adult intraocular melanoma [48]. GNAQ/GNA11 muta-

tions drive MAPK, and sometimes non-canonical signaling, and liver metastasis dominates mortality [49]. Multi-omics secretome work showed VGF upregulated in Gαq-mutant UM, controlled by Gαq/MEK/CREB, and prognostic for overall and disease-free survival [10]. VGF knockdown reduced growth and liver colonization; recombinant/secreted VGF bound TGFBR2, activated TGF-β/SMAD, induced endothelial-mesenchymal-transition-related genes, and activated hepatic stellate cells, which reciprocally enhanced invasion [10]. Combined Gαq and MEK inhibition reduced tumor burden, and VGF neutralization was proposed as adjunctive therapy [10]. This is one of the clearest examples of a VGF–TGFBR2 physical interaction driving stromal metastasis, separable from C3AR1-centric peptide biology.

5.4 Adrenocortical carcinoma

ACC is rare, aggressive, and lacking validated blood/protein biomarkers [50]. TCGA plus GTEx analysis (79 ACC, 128 normal adrenal) plus IHC validation showed VGF elevation in ACC versus normal cortex, association with advanced stage, nodes, metastasis, and poor OS [42]. Immune deconvolution linked VGF with Th2, T-helper, neutrophil, and CD8 infiltrate patterns, and GSEA highlighted cytokine-receptor interaction and PI3K-Akt [42]. Because ACC derives from steroidogenic cortex with neuroendocrine admixture, VGF likely reflects secretory phenotype plus PI3K/Akt–driven survival [42]. Proposed uses include IHC stratification, circulating VGF/peptide ELISA, and combination with mitotane/checkpoint approaches-though current data are exploratory.

5.5 Prostate cancer

Prostate bioinformatics from TCGA and GEO (including GSE55945, GSE21032) reported VGF upregulation in cancer versus normal, higher in advanced stage, inverse correlation with methylation, and shorter progression-free survival in low-methylation/high-expression groups [9]. Pathway enrichment includes GnRH, RIG-I-like receptor, and MAPK; transcription-factor regression identifies SP1, MAZ, NR3C1, CREB1 [9]. Experimental hypoxia studies show VGF promotes migration/invasion via PI3K/Akt, consistent with castration-resistant and hypoxic phenotypes [9]. In a screening of key genes related to radiosensitivity, VGF was identified as one of the top 20 genes [51]. Survival analysis showed that higher levels of VGF expression had a significantly reduced progression-free interval after radiotherapy [51]. Since prostate nerves and neuroendocrine transdifferentiation are increasingly tied to aggressive disease, VGF could mark treatment-related neuroendocrine progression (t-NEPC). In fact, single-cell sequencing data [52] showed that VGF expression is mainly observed in prostate cancer cells with neuroendocrine features (Fig. 1C). Bulk RNA-seq data also showed that t-NEPC patients showed a drastic elevation of VGF mRNA expression (Fig. 1B). However, current data are mostly bioinformatics plus mechanistic cell models, and prospective IHC/serum validation is needed.

5.6 Oral, laryngeal, and head/neck squamous cell carcinoma

OSCC/HNSCC profiling shows VGF upregulation, association with T3/T4 or node-positive disease, and worse survival; miR-432-5p targets VGF, and IL23R expression inversely correlates with VGF, suppressing motility when restored [43]. Laryngeal squamous cell carcinoma reports reduced secretogranin VGF expression in some cohorts, indicating site-specific directionality and the need for standardized antibodies/isoform assays [53]. In HNSCC overall, VGF may track with immune suppression and exosome release pathways, suggesting utility in stratification for immunotherapy or anti-myeloid combinations [43].

5.7 Pancreatic ductal adenocarcinoma and TLQP-21 therapeutics

PDAC expresses VGF in pancreas and neural tissues and is associated with severe pain, depression, and cachexia [11]. Counterintuitively, high bulk VGF can correlate with better survival in some datasets, and TLQP-21 therapy in orthotopic mice reduced tumor size, enhanced gemcitabine efficacy, increased overall survival, relieved allodynia and depression-like behavior, and reduced muscle wasting [11]. The mechanism centered on suppression of M2-like tumor-associated macrophages through C3AR1 and C1QBP rather than direct tumor killing [11]. This model is important because it separates "block VGF" (appropriate where precursor/secreted full-length drives resistance/metastasis) from "administer TLQP-21" (appropriate where a defined peptide reprograms myeloid cells). It also addresses quality-of-life symptoms-pain, mood, cachexia-that standard PDAC therapeutics ignore. In addition, proteomic analysis and in vitro modelling of perineural invasion in pancreatic cancer identified VGF upregulation with IHC validation, directly linking VGF to the neural

crosstalk underlying PDAC pain and neurotrophic progression [64].

5.8 Neuroendocrine neoplasms: pituitary, gastroenteropancreatic, and pNEN

VGF is physiologically expressed in pituitary, islets, and gut neuroendocrine cells, so it is a natural marker in neuroendocrine neoplasms [29]. Pituitary tumor literature is indirect: NGF signaling affects lactotrope differentiation/prolactinoma biology [54], and VGF peptides regulate hypothalamic–pituitary axes [4, 5]; therefore, systematic VGF IHC in pituitary adenoma subtypes is comparatively sparse and should be a research priority. In pancreatic neuroendocrine neoplasms (pNEN), lncRNA H19 binds VGF and promotes progression via PI3K/Akt/CREB, linking a noncoding RNA, secretory granin, and mTOR-adjacent signaling [55]. Gastroenteropancreatic NENs are highly vascular and VEGF-driven therapeutically (sunitinib, surufatinib) [56], but VGF's role is distinct: peptide secretion, hormonal symptoms, and possibly complement/TrkB crosstalk [39]. VGF could help subtype grading or hormone-independent symptom burden, but it should not be merged with VEGF angiogenesis markers. Historically, proVGF-derived peptides were shown to be produced in human neuroendocrine cells from early development and to increase in hyperplasia and neoplasia, establishing the foundation for VGF as a neuroendocrine neoplasm marker [62].

5.9 Glioma and endometrial cancer

Human Protein Atlas prognostic summary labels VGF unfavorable in glioma and endometrial carcinoma [30]. Given VGF's neural origin, glioma relevance may involve tumor–neuron signaling, HSPA8 surface interactions, C3AR1-mediated complement inflammation, and chemoresistance [7, 32, 36]. Mechanistic evidence in glioma is, in fact, stronger than transcriptomic prognostics alone. Wang et al. demonstrated reciprocal paracrine signaling between glioblastoma stem cells (GSCs) and their differentiated tumor cell (DGC) progeny: DGCs preferentially express and secrete BDNF, which acts on NTRK2/TrkB expressed by GSCs, and the downstream mediator of this axis—selectively expressed by GSCs-is VGF [60]. VGF serves a dual role in the glioblastoma hierarchy, promoting GSC survival and stemness in vitro and in vivo while simultaneously supporting DGC survival and inducing DGC secretion of BDNF, thereby closing a BDNF–NTRK2–VGF feed-forward loop that fuels tumor growth [60]. This circuit is consistent with the marked enrichment of NTRK2 in TCGA lower-grade glioma and glioblastoma (median RSEM ≈36,000 and ≈8,500, respectively; PanCancer Atlas, cBioPortal), and provides a mechanistic basis for the unfavorable VGF prognostic label in glioma [30], making fragment-resolved VGF targeting a testable strategy in NTRK2-high glioma. Beyond paracrine signaling, MEG3 in glioma stem cells promotes glioblastoma angiogenesis through FUBP3-mediated VGF expression, adding a GSC-intrinsic angiogenic dimension to VGF biology in glioma [66]. Endometrial data are principally transcriptomic/prognostic [30]; mechanistic studies should examine PI3K/Akt (common in endometrioid carcinoma), estrogen-related neuroendocrine differentiation, and macrophage complement signaling. Both sites warrant fragment-resolved assays rather than total VGF alone.

5.10 Other potential sites

Based on pan-cancer upregulation and granin biology, VGF may appear in gastric, colorectal, ovarian, and thyroid neuroendocrine/non-neuroendocrine tumors, but primary cancer-specific evidence is currently thinner than for lung, breast, UM, ACC, prostate, oral, and PDAC. Reviews of VGF biomarkers note multiple CSF and endocrine fragments relevant to diagnostics [3, 57]; translating those to oncology requires tissue-specific peptide mapping. Emerging evidence also extends VGF to hilar cholangiocarcinoma, where cancer-associated Schwann cell-derived VGF augments epithelial–mesenchymal transition and perineural invasion (conference abstract) [65].

6. Therapeutic strategies

6.1 Anti-VGF neutralizing antibodies or trapping

Where full-length secreted VGF drives resistance/metastasis (lung neuroendocrine, UM, possibly ACC/breast brain), neutralizing antibodies against precursor/secreted fragments could reduce paracrine signaling. Lung models explicitly propose anti-VGF mAbs for TKI-resistant neuroendocrine disease [8]. Challenges: which epitopes neutralize TGFBR2-binding vs complement peptides? Total blockade may remove beneficial TLQP-21 effects; fragment-selective antibodies are preferable.

6.2 TLQP-21 and TLQP mimetics

TLQP-21 is beneficial in PDAC via C3AR1/C1QBP myeloid suppression, gemcitabine sensitization, analgesia, and antidepressant-like effects [11, 32, 33].

Design issues: short half-life, disorder, proteolysis; C-terminal amidation/S20A substitutions alter C3AR1 potency. Stabilized helicogenic analogs, depot formulations, or C3AR1-biased agonists may reproduce macrophage reprogramming without anaphylaxis. TLQP mimetics could be tested in glioma, HNSCC, and cold tumors with C3AR1-high myeloid infiltrate. A critical translational caveat is that human TLQP-21 is a low-potency partial C3aR activator on human primary macrophages, whereas the rodent peptide is more potent; efficacy in murine PDAC models may therefore not extrapolate directly to humans without fragment- and species-optimized design [61].

6.3 C3AR1/C1QBP modulators

If TLQP actions are C3AR1-dependent, small-molecule C3AR1 antagonists/inverse agonists could block protumor complement loops; conversely, controlled C3AR1 agonism with TLQP analogs may repolarize macrophages. Choice depends on tumor: in PDAC M2-dominant TME, TLQP/C3AR1 bias toward M1 may help; in C3a-driven suppressive myeloid cancers, antagonism may help. Patient selection should likewise follow receptor expression topology rather than tumor-cell receptor status. C3AR1-targeted approaches, agonist or antagonist alike, are in practice myeloid-directed therapies and belong in tumors with C3AR1-high myeloid infiltrates, whereas the ubiquitous C1QBP expression in tumor and stroma makes direct C1QBP targeting inherently non-selective. C1QBP is not irreversibly intracellular. However, stress and inflammatory stimulation can drive its re-localization to the cell surface of activated stromal and tumor cells, and this stress-restricted exposure offers a narrow but realistic window for peptide- or antibody-based targeting and imaging in selected contexts [68, 69]. Beyond such contexts, C1QBP modulators remain premature pending cancer validation.

6.4 TGFBR2/SMAD and stromal intersection

UM data support VGF-TGFBR2 interaction and stellate activation [10]. Therapeutics could combine Gαq/MEK inhibition with TGF-βR inhibitors or anti-fibrotic stellate targeting; VGF neutralizing antibodies might substitute for part of TGFBR2 blockade with less systemic TGF toxicity. Caution: TGF-β inhibition can promote inflammation/autoimmunity and, in some contexts, tumor escape; biomarker selection (Gαq/MEK-high, TGFBR2-interaction-positive) is essential.

6.5 Epigenetic and MAPK/CREB combinations

HDAC1 occupies VGF in lung [7, 44]; MEK/CREB drive VGF in UM [10]. Combinations of HDAC inhibitors with care (because they can induce VGF), MEK inhibitors with anti-VGF, or CREB pathway inhibitors in neuroendocrine resistance are rational. In EGFR-TKI relapse, adding VGF silencing/resilience to TWIST1/EMT may restore TKI sensitivity in selected neuroendocrine converted adenocarcinomas [8].

6.6 PI3K/Akt/mTOR and neuroendocrine NENs

The most direct therapeutic entry point in neuroendocrine neoplasms comes from pathway concordance. In pNEN, lncRNA H19 drives VGF through PI3K/Akt/CREB signaling [55], and VGF biology in adrenocortical carcinoma is similarly linked to PI3K/Akt activity [42]. These observations argue for combining mTOR inhibition (everolimus, already established in pNEN) or PI3K-directed agents with VGF modulation, since VGF signaling converges on the same axis. Because neuroendocrine tumors are also frequently managed with VEGF-directed antiangiogenic therapy [56], trials that incorporate VGF endpoints should track VEGF independently, so that secretory-granule and vascular biomarkers are not conflated.

7. Limitations and controversies

This review article has the following limitations. First, receptor heterogeneity: C3AR1 was validated for TLQP-21, but C1QBP /HSPA8 remained a candidate. TGFBR2 showed context-specific effects, and TrkB was shown for TLQP-62. Therapies cannot assume one receptor. In addition, species differences in TLQP-21 potency at C3AR1-low-potency partial agonism on human primary macrophages-limit direct extrapolation of rodent therapeutic data to patients [61]. Second, precursor vs peptide direction: high total VGF may be protumor, yet TLQP-21 can be antitumor in PDAC; biomarker cutoffs must define fragment. Third, antibody and mass-spec standards: the granin precursors share motifs; IHC validation across clones is inconsistent. Fourth, confounding with neuroendocrine differentiation: VGF marks neuroendocrine phenotype, so "prognostic" signal may reflect histology rather than causality; multivar-

iate adjustment for Ki-67, synaptophysin/chromogranin, and lineage is mandatory. Fifth, VGF vs VEGF confusion in databases and grant writing must be actively prevented in protocol titles. Lastly, most cancer data are bioinformatics or single-cohort; ACC, UM, lung, breast, PDAC, oral have functional support, but prostate/pNEN/glioma/endometrial need prospective validation.

8. Future research agenda

a. Generate fragment-resolved assays (ELISA/MS) for TLQP-21, TLQP-62, NERP-1/2, full-length VGF in plasma/CSF/tissue.
b. Map PCSK1/2 and convertase splice states in each tumor type to predict peptide output.
c. Conduct C3AR1, C1QBP , TGFBR2, TrkB, HSPA8 companion-receptor scoring for trial eligibility.
d. Test anti-VGF antibody vs TLQP-21 mimetic head-to-head in orthotopic brain/liver/pancreas models to resolve antagonist versus agonist paradigms.
e. Run biomarker-driven trials in EGFR-TKI-resistant neuroendocrine lung, Gαq UM liver-metastatic setting, ACC, HER2/TN breast brain-metastatic risk, and TLQP-responsive PDAC pain/cachexia.
f. Integrate single-cell multi-omics to separate tumor-cell autocrine VGF from stromal/immune VGF responses.

9. Conclusions

VGF is a neurosecretory granin precursor with cancer-relevant peptide signaling rather than a single-receptor oncogene. Its strongest tumor associations are in neuroendocrine and neuron-interacting malignancies-SCLC/LCNEC, EGFR-TKI-resistant adenocarcinoma, uveal melanoma liver metastasis, breast brain metastasis, ACC, prostate and oral squamous cancer, and selected PDAC/NEN/glioma/endometrial cases. Receptors/binding partners are fragment-specific: C3AR1 is the lead TLQP-21 receptor; C1QBP and HSPA8 are modulatory/candidate; TrkB mediates TLQP-62 neuroplasticity; TGFBR2 is a disease-specific effector in Gαq melanoma; integrin/STAT3 and CREB/MAPK are upstream regulators. Therapeutic logic must distinguish anti-VGF blockade (where precursor drives resistance/stromal metastasis) from TLQP peptide replacement (where C3aR1/C1QBP myeloid reprogramming, analgesia, and chemo sensitization are desired). Moreover, receptor identity must be read together with receptor expression topology: C3aR1 marks the myeloid compartment rather than malignant epithelium, making TLQP-21-based strategies myeloid-reprogramming rather than tumor-cell-directed, whereas ubiquitous C1QBP expression restricts direct targeting to contexts of stress-induced surface exposure [68, 69]. Translational extrapolation is further limited by species pharmacology: human TLQP-21 is a low-potency partial C3aR agonist on human primary macrophages, so murine efficacy must be re-derived with human- and fragment-optimized molecules [61]. Finally, the VGF/VEGF nomenclature collision remains a practical hazard for database annotation, grant titles, and trial design. With fragment-resolved biomarkers and companion stromal-receptor profiling, VGF could move from a neuroendocrine IHC curiosity to a stratified target in several difficult human cancers.

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