REVIEW

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The Functional Interplay among *GAD2*, *GABRG2*, and *CACNA1G* Genes in Cancers

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Abstract

The GABAergic system, commonly known as the inhibitory system in the central nervous system, also plays a crucial role in cancer development. **Objective:** This article reviews the complex interactions between the GABAergic system and tumor progression, emphasizing the *GAD2*, *GABRG2*, and *CACNA1G* genes. **Method:** A comprehensive literature review was conducted to assess current evidence regarding the involvement of *GAD2*, *GABRG2*, and *CACNA1G* genes in promoting cancer development through enhanced tumor growth, cell survival, and increased intracellular calcium levels. **Result:** While GABA generally suppresses neural activity, it can paradoxically promote cell proliferation and survival in cancer cells. The *GAD2* gene produces an enzyme that helps create GABA. Higher levels of *GAD2* expression have been linked to tumor growth and survival in several types of cancer. The *GABRG2* gene encodes a subunit of the GABA-A receptor. When this receptor is activated, it can cause depolarization and activate signaling pathways that promote cancer cell growth. The *CACNA1G* gene encodes a subunit of a calcium channel that controls calcium ion entry into cells. Higher levels of *CACNA1G* expression are frequently found in various cancers, contributing to tumor development by increasing intracellular calcium levels. **Conclusion:** This article examines the role of *GAD2*, *GABRG2*, and *CACNA1G* genes in cancer progression, highlighting their interactions in promoting tumor growth and survival. A deeper understanding of the molecular mechanisms underlying GABA signaling, its receptors, and the associated genes in cancer could lead to the identification of new therapeutic targets and the development of more effective treatments. Further research is essential to elucidate the detailed mechanisms driving cancer development and progression.

Keywords: GABAergic system- genes interplay- molecular mechanism

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Introduction

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system (CNS) [1]. It exerts its effects by binding to two distinct receptor classes: GABA Type-B reseptors, chloride ion channels, and GABA Typers, which are metabotropic G-protein-coupled receptors [2]. GABA is synthesized from glutamate through the catalytic activity of the glutamate decarboxylase enzymes GAD65 and GAD67 [3]. During the nervous system development, GABA plays a pivotal role in regulating essential cellular processes such as proliferation, differentiation, migration, and apoptosis. Interestingly, GABA and its receptors, particularly GABA-A and GABA-B, are also expressed in non-neuronal peripheral tissues [4], including the oral cavity, lungs [5], pancreas [6], liver [7], and stem cells [8]. These findings suggest that the GABAergic system has broader physiological functions beyond neurotransmission, contributing to cellular homeostasis in various tissues.

Emerging evidence also indicates that the expression of the GABAergic system is significantly elevated in various cancers, such as colon, lung, stomach, and oral squamous cell carcinoma, compared to normal tissues [9-12]. The upregulation of GABA through the action of glutamate decarboxylase (GAD) enhances the binding of GABA to its receptors. The activation of GABA receptors, particularly those encoded by *GABRG2*, has been associated with the activity of voltage-gated calcium channels (VGCCs), specifically the Cav3.1 channel encoded by the *CACNA1G* gene. These channels are critical in regulating intracellular calcium levels, essential for cell proliferation, survival, and tumor progression. Overexpression of *CACNA1G*

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has been reported in various types of cancers, including breast, lung, prostate, and melanoma, where it facilitates calcium influx and promotes tumor growth [13]. The findings highlight a potentially critical interplay among *GAD2*, *GABRG2*, and *CACNA1G* in cancer development and progression. These genes may collectively contribute to tumor growth and malignancy by influencing the signaling pathway processes. This review explores these genes' functional roles and interconnections, shedding light on their contributions to cancer progression and their potential as therapeutic targets.

GAD2, GABRG2, and CACNA1G Roles in GABAergic System

The GABAergic system primarily comprises GABA, GABA transporters, GABA receptors, and GABAergic neurons [4]. GABA plays a crucial role in maintaining the balance between excitation and inhibition in the nervous system [14]. GABA is synthesized from glutamate by the enzyme glutamate decarboxylase (GAD), which exists in two isoforms: GAD65 and GAD67 [15]. These enzymes are encoded by the *GAD2* and GAD1 genes, respectively. GAD65, encoded by *GAD2*, is particularly important for activity-dependent GABA synthesis and vesicular storage, ensuring rapid neurotransmitter release during synaptic transmission [16-18]. GABA synthesis primarily occurs through two distinct pathways: the GABA shunt and the glutamate-GAD pathway [19, 20]. The glutamate-GAD pathway, which involves the direct conversion of glutamate to GABA by the enzyme glutamate decarboxylase (GAD), is the predominant pathway in the CNS [21, 22]. GAD is primarily expressed in GABAergic neurons within the brain and spinal cord, where it plays a crucial role in regulating neuronal excitability and maintaining synaptic balance [23, 24].

In contrast, the GABA shunt pathway is more prominent in non-neuronal cells, such as those found in various peripheral tissues and organs [4, 25, 26]. In this pathway, glucose enters the Krebs cycle, metabolizing it into α-ketoglutarate. Subsequently, α-ketoglutarate is transaminated by the enzyme α-oxoglutarate transaminase (GABA-T) to form glutamate. GAD then decarboxylates this glutamate to produce GABA. The produced GABA can be further metabolized into succinate through the actions of GABA transaminase (ABAT) and succinate semialdehyde dehydrogenase (SSADH). This succinate subsequently re-enters the tricarboxylic acid cycle (TCA) to generate ATP, contributing to cellular energy metabolism [19, 27-29, 30].

GABA exerts its inhibitory effects primarily through GABA-A receptors, which are ligand-gated chloride ion channels. These receptors are pentameric complexes of various subunits, including α, β, and γ subtypes. In humans, 19 subunit genes have been identified, encoding six α (alpha1-6), three β (beta1-3), three γ (gamma1-3), three ρ (rho1-3), and one each of δ (delta), ε (epsilon), π (pi), and θ (theta) subunits [31]. Adult GABA-A receptors typically combine α1, β2, and γ2 subunits, forming a distinct receptor structure. The γ2 subunit, encoded by the *GABRG2* gene, is essential for receptor clustering and localization, ensuring accurate synaptic positioning through its interaction with the gephyrin protein [31, 32]. The binding of GABA to GABA-A receptors induces a conformational change, allowing chloride ions to enter the neuron. Consequently, it hyperpolarizes the neuronal membrane, decreasing excitability and effectively dampening excessive neuronal activity [32].

Voltage-gated calcium channels (VGCCs) are crucial for cellular function, complementing GABAergic signaling by regulating calcium homeostasis and intracellular signaling. They act as key transducers of membrane potential changes into intracellular calcium signals, influencing various cellular processes, including cell cycle progression, proliferation, differentiation, and apoptosis [13, 33, 34]. VGCCs are composed of multiple subunits, with the α1 subunit forming the pore that allows calcium ions to flow into the cell. This influx of calcium ions is a crucial second messenger, activating various signaling pathways that control diverse cellular functions. The VGCC family encompasses five major subtypes: L-type, R-type, N-type, P/Q-type, and T-type, each with distinct properties and distributions [33, 34]. The T-type VGCC, specifically the Cav3.1 subtype encoded by the *CACNA1G* gene, is particularly important in neurons and other excitable cells. It is critical in regulating neuronal excitability, pacemaker activity, and other physiological processes [13, 34].

Dysregulation of GABAergic in Cancers
GAD2 expression in cancers

The expression of *GAD2* varies significantly across cancer types. High levels are observed in neuroendocrine carcinoma (58.3%) and pancreatic tumors (63.2%), while lower levels are found in pulmonary neuroendocrine tumors (11.1%) and granular cell tumors (37.0%) [35]. *GAD2* overexpression in gallbladder adenocarcinoma correlates with poor survival outcomes, implicating its role in gallbladder cancer progression [36]. In contrast, *GAD2* expression is reduced in gliomas compared to normal glial cells, where higher levels are associated with improved overall and progression-free survival, highlighting its potential as a prognostic biomarker [37-39]. In oral squamous cell carcinoma (OSCC), *GAD2* facilitates metabolic reprogramming by converting glutamate to γ-aminobutyrate, differentiating malignant cells from healthy tissues and emphasizing its role in cancer-associated metabolic shifts [40]. Additionally, *GAD2* expression in breast cancer tissues and cell lines suggests its involvement in invasion and metastasis [41, 42]. Pediatric brain tumors exhibit downregulated *GAD2* expression, with higher levels correlating with better survival outcomes, supporting its diagnostic and prognostic utility [39].

GABRG2 Expression in Cancers

The *GABRG2* gene, encoding the γ2 subunit of the GABA-A receptor, has also been linked to various cancers. In glioblastoma, reduced *GABRG2* expression correlates with poor prognosis and impacts tumor growth via GABA receptor-related pathways [43-45]. In colon adenocarcinoma (COAD), *GABRG2* expression is associated with survival outcomes, while in

hypopharyngeal carcinoma co-occurring with esophageal carcinoma, it serves as a key diagnostic marker for evaluating comorbidity risks [46, 47]. Furthermore, in laryngeal cancer, *GABRG2* is part of the competitive endogenous RNA (ceRNA) regulatory network implicated in recurrent disease, though its molecular contributions to cancer require further elucidation [48].

CACNA1G Expression in Cancers

The *CACNA1G*, encoding the Cav3.1 subunit of T-type calcium channels, plays a critical role in calcium signaling, which is often dysregulated in cancer. Elevated CaV3.1 expression enhances intracellular calcium influx, driving processes like tumor proliferation, migration, and drug resistance [33]. ONCOMINE analyses reveal increased *CACNA1G* expression across multiple cancers, including sarcoma, colorectal, uterine, prostate, lung, and breast [13]. In laryngeal squamous cell carcinoma, *CACNA1G* knockdown or treatment with the CaV3 channel blocker mibefradil reduces cell proliferation by inducing cell cycle arrest [49]. Similarly, Cav3.1 channels are uniquely expressed in melanoma cells, mediating constitutive calcium influx critical for tumor viability and growth [50].

The Interplay of GAD2, GABRG2, and CACNA1G in Cancer Progression

GABA acts as an excitatory neurotransmitter in the initial phases of brain development. GABA will bind to GABA-A receptors on immature neurons and initiate the release of chloride ions from the cell. Elevated intracellular chloride levels trigger the efflux of chloride ions from the cell due to the activity of the NKCC1 transporter [51]. The release of chloride ions causes cell depolarization, subsequently activating the inflow of sodium and calcium ions via voltage-gated ion channels. Elevating intracellular calcium concentrations resulting from GABA-A receptor activation is crucial for numerous neuronal developmental processes, including proliferation, migration, differentiation, synapse maturation, and programmed cell death [14]. Consequently, GABA functions as a trophic element that facilitates the development and maturation of neurons. [52, 53]. The reduction in intracellular chloride concentration causes a shift in the chloride equilibrium potential to become more negative. As a result, when GABA binds to its receptor, chloride ions enter the cell, causing hyperpolarization. Thus, the effect of GABA is changed from excitatory to inhibitory [54].

Recent studies show that cancer cells express GABA-A receptors and exhibit electrophysiological characteristics similar to immature neurons, indicating that the processes governing GABA's function in brain development may similarly influence tumor growth and progression. Cancer cells frequently display alterations in the expression and functionality of ion channels, which may contribute to uncontrolled proliferation, invasion, and metastasis [14, 55]. Cancer cells have a depolarized membrane potential compared to normal cells, which can promote cell proliferation [56].

GABA levels that are elevated in cancer cells can promote the growth and survival of tumors. When GAD65, encoded by *GAD2*, is activated in prostate cancer, more GABA is produced, thus keeping androgen receptors in the nucleus, which in turn promotes the proliferation of cancer cells [57]. Due to its location at the presynaptic terminal and its role in GABA synthesis for vesicle release, *GAD2* plays a significant role in the cellular response to stress, which is a prevalent occurrence in the tumor microenvironment [17].

The Warburg effect is the preference for glycolysis even when there is enough oxygen present in cancer cells, like OSCC, due to impairment to mitochondrial respiration activity. Because of the disruption of metabolic pathways, synthesis GABA by GAD1 in the mitochondria accumulates due to this inhibition of the TCA cycle in the mitochondria. This metabolic reprogramming causes glutamate that ought to be broken down by the mitochondria's TCA to be diverted and processed via a different pathway that uses the cytoplasmic *GAD2* to synthesize GABA [40]. *GAD2* is activated through phosphorylation, which enhances its ability to synthesize GABA from glutamate. This process is particularly evident in castration-resistant prostate cancer (CRPC), where *GAD2* activation supports tumorigenesis by regulating androgen receptor signaling [57, 58]

Several studies have demonstrated that GABA can stimulate cell proliferation via GABA type A receptors (GABAAR) in various cancer types, including hepatocellular carcinoma (HCC) [9], prostate cancer [59], gastric cancer [12], breast cancer [60, 61], pancreatic ductal adenocarcinoma (PDAC) [62], and oral squamous cell carcinoma (OSCC) [63]. The θ and α3 subunits are overexpressed in HCC tissues compared to adjacent non-tumor liver tissues. In breast cancer, the overexpression of the α3 subunit has been reported to enhance cancer cell migration, invasion, and metastasis [61]. In human thyroid cancer, GABA receptor expression is higher in tumor tissues than in normal thyroid tissues [64]. However, research on the γ2 subunit in cancer remains limited despite its high expression observed in HNSCC [48, 65].

The expression of GABA-A receptors is tightly regulated and occurs only when required. Their localization and stabilization on the cell membrane are controlled by the γ2 subunit, encoded by the *GABRG2* gene. An upregulation of the γ2 subunit can disrupt the regulation of receptor expression on the membrane, leading to an increased presence of GABA-A receptors at the membrane surface [18, 32]. Activating GABAA receptors in cancer cells can trigger calcium ion influx, activating various signaling pathways that promote cell proliferation and invasion. The excitatory properties of GABA in cancer, caused by chloride efflux and cell depolarization, lead to an elevation in intracellular calcium concentration [66]. Elevated expression of the *CACNA1G* gene results in increased intracellular calcium influx [67]. Alterations in electrical charges across the cell membrane are essential for sustaining cellular homeostasis in physiological and pathological conditions [68]. The impact of slight variations in calcium could regulate specific cell functions, whereas a substantial alteration of calcium could be responsible for cell proliferation and motility or even cell

apoptosis [13]. Dysregulation of calcium is an emerging feature of cancer and is crucial in the initiation and progression of malignant diseases [69].

The studies investigating the role of Cav3.1 T-type calcium channels in cancer progression highlight its significant involvement in various cancer types. In prostate cancer, upregulation of Cav3.1 positively correlates with tumor progression, with knockdown of Cav3.1 inhibiting cell proliferation, migration, and invasion through the suppression of the AKT signaling pathway, emphasizing its crucial role in cancer progression [70]. Similarly, in hepatocellular carcinoma, Cav3.1 contributes to cell proliferation, and its inhibition using mibefradil reduces proliferation by increasing phosphorylated ERK1/2, indicating the involvement of the ERK1/2 signaling pathway in this process [71]. In retinoblastoma, Cav3.1 overexpression is linked to increased cell viability, and inhibition of EGFR reduces both Cav3.1 expression and current density. At the same time, MAPK inhibition also decreases Cav3.1 currents, suggesting that Cav3.1 regulates the EGFR-MAPK signaling pathway to promote cancer cell viability [72]. These studies underscore the pivotal role of Cav3.1 in cancer, influencing cell proliferation, migration, and invasion through distinct signaling pathways such as AKT, ERK1/2, and MAPK, making it a potential therapeutic target in cancer treatment.

Significantly, the overexpression of Cav3.1 is strongly associated with the activation of pro-proliferative pathways, whereas its inhibition or downregulation leads to reduced proliferation and, in some cases, increased cell death (apoptosis). This ability of Cav3.1 channels to modulate cellular calcium dynamics emphasizes the critical role of calcium regulation in cancer progression.

In summary, Figure 1 visually represents the interplay between the *GAD2*, *GABRG2*, and *CACNA1G* genes in promoting cancer cell proliferation. It highlights how their interactions alter cellular ion dynamics, including increased calcium influx and cell depolarization, contributing to tumor growth and progression.

Potential Therapeutic Strategies and Challenges

Targeting the GABAergic system, particularly through GABA receptors and calcium channels like Cav3.1, is a promising cancer therapy strategy. This strategy involves manipulating GABA receptors, with both GABA receptor agonists and antagonists offering potential direct therapeutic applications. For GABA-A receptors (GABAAR), functional activity can be enhanced by agonists such as benzodiazepines, barbiturates, zolpidem, and propofol. In contrast, antagonists like bicuculline, flumazenil (which binds to the GABAAR site), and picrotoxin (which binds allosterically) have been shown to attenuate receptor activity [73]. Notably, GABAAR antagonists, such as picrotoxin and flumazenil, have demonstrated anti-proliferative effects in prostate and other cancers, potentially through pathways involving calcium influx and apoptosis regulation [74, 75]. However, it is important to recognize the dual nature of these agents,

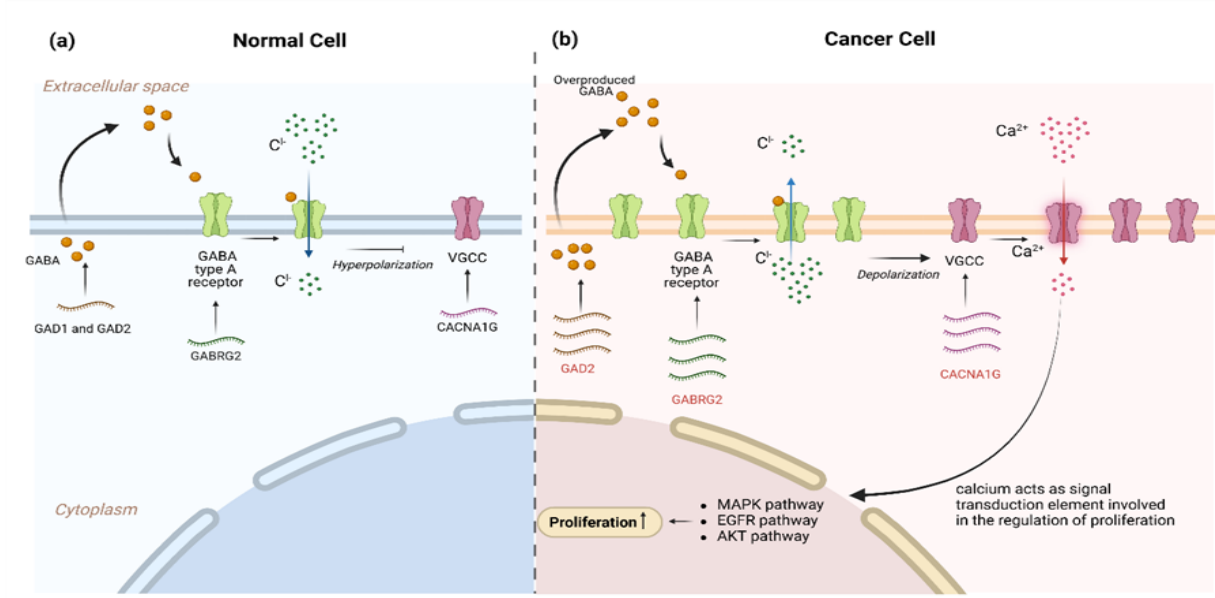

Figure 1. Schematic Representation of the Functional Interplay among *GAD2*, *GABRG2*, and *CACNA1G* in Normal Cell and Cancer Cell (Created in BioRender). (a) In normal cells, GABA is produced by the GAD65 and GAD67 enzymes, which are encoded by the *GAD2* and GAD1 genes, respectively [15]. Once synthesized, GABA binds to GABA-A receptors, triggering the activation of chloride channels. This activation results in the influx of chloride (Cl^-) ions into the cell, leading to hyperpolarization. This inhibitory effect plays a crucial role in regulating normal cellular functions and preventing uncontrolled cell growth [31]. (b) In cancer cells, *GAD2* is overexpressed, leading to excessive GABA production [57]. Additionally, overexpression of *GABRG2* enhances the surface expression of GABA-A receptors [31, 32]. In these cells, the activity of the sodium-potassium-chloride cotransporter (NKCC1) is also upregulated, causing an accumulation of chloride ions within the cell [51]. Consequently, GABA binding to GABA-A receptors triggers chloride efflux rather than influx, which results in membrane depolarization [14, 56]. This depolarization activates voltage-gated calcium channels (VGCC), encoded by *CACNA1G* gene, causing an excessive influx of calcium ions (Ca^{2+}) [68]. The increased intracellular calcium concentration subsequently activates signaling pathways, such as MAPK, EGFR, and AKT, which promote cell proliferation [72-74].

as while GABAAR agonists may offer therapeutic benefits, they have also been associated with the facilitation of tumor progression through the activation of intracellular signaling pathways and alterations in cellular morphology, underscoring the therapeutic potential and complexity of targeting GABAergic signaling in cancer. This approach must be taken cautiously, particularly given that such agents are commonly utilized in perioperative settings, where they may influence tumor cell behavior post-surgery [76]. Moreover, inhibiting Cav3.1 T-type calcium channels has emerged as a promising therapeutic approach, as members of the CaV3 subfamily have been identified in various malignancies, including carcinomas, brain tumors, and hematological cancers. These channels are often involved in pro-survival and pro-proliferative signaling pathways, highlighting their potential as targets for anticancer therapy [77]. However, clinical application remains limited despite the encouraging results of T-type calcium channel blockers like mibefradil, KYS05041, and NNC 55-0396 in preclinical models, which show varying degrees of efficacy across different cancer types. This is mainly due to the absence of selective Cav3.1 inhibitors and the risk of cardiotoxic and neurological side effects, often linked to off-target interactions with other ion channels, such as L-type calcium channels [78].

In conclusion, this review highlights the critical interplay among *GAD2*, *GABRG2*, and *CACNA1G* in cancer development and progression. *GAD2* facilitates GABA synthesis, enhancing GABA signaling, while *GABRG2* mediates receptor activation, activating voltage-gated calcium channels (VGCC) encoded by *CACNA1G*. By regulating Cav3.1 calcium channels, *CACNA1G* modulates intracellular calcium levels, which drives cell proliferation, survival, and tumor progression by activating downstream oncogenic pathways such as AKT, EGFR, and MAPK. The evidence underscores the significance of these genes in regulating calcium homeostasis and tumorigenic signaling, suggesting their potential as interconnected biomarkers and therapeutic targets in various cancers. Further investigation into their mechanistic roles is essential to advance cancer diagnostics and develop targeted therapeutic strategies.

Author Contribution Statement

Sagung Rai Indrasari, Salma Darmayanti, Adila Zafrullah, Nina Sakina Lessy: Writing - Original draft preparation. Sofia Mubarika Haryana, Ahmad Hamim Sadewa: conceived ideas and supervised the work. Risky Oktriani: Writing – Review and Editing.

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Ethical Declaration

This study reported only data that had already been published. We had no direct access to the original data used in the included studies for the review. Therefore, no ethical approval was needed.

Data Availability

This work incorporates data previously published by other authors, with all data included in the findings section.

Conflict of Interest

The authors declare that there are no conflicts of interest concerning the content of the present study.

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