Review

The Emerging Roles of π Subunit-Containing GABA$_A$ Receptors in Different Cancers

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Abstract

Cancer is one of the leading causes of death in both developed and developing countries. Due to its heterogenous nature, it occurs in various regions of the body and often goes undetected until later stages of disease progression. Feasible treatment options are limited because of the invasive nature of cancer and often result in detrimental side-effects and poor survival rates. Therefore, recent studies have attempted to identify aberrant expression levels of previously undiscovered proteins in cancer, with the hope of developing better diagnostic tools and pharmaceutical options. One class of such targets is the π-subunit-containing γ-aminobutyric acid type A receptors. Although these receptors were discovered more than 20 years ago, there is limited information available. They possess atypical functional properties and are expressed in several non-neuronal tissues. Prior studies have highlighted the role of these receptors in the female reproductive system. New research focusing on the higher expression levels of these receptors in ovarian, breast, gastric, cervical, and pancreatic cancers, their physiological function in healthy individuals, and their pro-tumorigenic effects in these cancer types is reviewed here.

Key words: Cancer, GABA$_A$ receptors, π subunit, female reproductive system

Introduction

Cancer is a broad term used to describe more than 277 different types of diseases (leukemia, melanoma, lymphoma, etc.) that occur in various regions of the body caused by uncontrolled mitotic cell division [1]. This uncontrolled growth and division of cells due to genetic mutations results in neoplasms (tumors); therefore, cancer is a (malignant) neoplastic condition. Mutations leading to cancer may arise due to genetic predispositions [2], environmental carcinogens [3], lifestyle choices (e.g., diet, excessive drinking, tobacco smoking, etc.) [4], radiation exposure [5], viral infections [6, 7], and epigenetic changes (e.g., histone modifications, DNA methylation, and microRNA dysregulation) [8]. Globally, there were an estimated 19.3 million diagnosed cases and approximately 10.0 million deaths in 2020 related to cancer, excluding nonmelanoma skin cancer [9]. Prostate and breast cancer are the most commonly diagnosed cancers in men and women, respectively [10]. Notably, a recent 25-year study revealed a significant increase in the mortality rate of patients with breast cancer in both developed and developing countries [11]. To curb the cancer mortality rate, current antineoplastic options include chemotherapy [12], radiotherapy [13], immunotherapy [14], hormone therapy [15], surgery [16], precision medicine [17], molecular targeted therapy [18], and stem cell transplantation [19]. However, due to the heterogenous and invasive nature of some types of cancer, therapy is not always feasible, leading to poor prognosis and survival rates [20, 21, 22, 23, 24, 25, 26, 27]. Therefore, current research is focused on previously undiscovered pathways and other factors (such as receptors) that are involved in cancer development in order to design newer and more effective antineoplastic agents. Recent studies have implicated γ-aminobutyric acid (GABA) type A receptors (GABA$_A$Rs), more specifically GABA$_A$ receptor containing the π subunit (GABRP), in cancer [28, 29]. Therefore, this review

highlights the existing knowledge of GABRP expression and function in healthy individuals and its potential role in cancer.

The GABA$_A$ receptors

GABA is the main inhibitory neurotransmitter of the central nervous system and it generates fast signaling neurotransmissions through the GABA$_A$Rs that are cys-loop ligand-gated ion channels comprising five subunits (the main receptor subtype contains two α, two β, and one γ subunit [α–β–α–β–γ]) enclosing a central chloride ion (Cl$^-$) pore in the brain [30]. To date, 19 subunits have been discovered in the human (α1–α6, β1–β3, γ1–γ3, δ, ε, θ, π, and ρ1–ρ3). When two molecules of GABA bind to the β$^+$/α$^-$ interface, they cause a conformational change in the receptor structure, resulting in the opening of channels permeable to Cl$^-$. This causes an influx of Cl$^-$ into the cell, resulting in hyperpolarization of the membrane and inhibition of neuronal signaling [31] (**Figure 1**). When GABA$_A$Rs are activated in healthy neurons, hyperpolarization may occur, only if the extracellular concentration of Cl$^-$ is greater than the intracellular concentration, resulting in an influx of Cl$^-$ into the cell. This Cl$^-$ homeostasis is maintained by two essential cation-chloride cotransporters, sodium-potassium-chloride cotransporter isoform 1 (NKCC1) and potassium-chloride cotransporter isoform 2 (KCC2). NKCC1 assimilates Cl$^-$ into the cell, whereas KCC2 expels Cl$^-$ from the cell [32]. In healthy neurons, KCC2 is expressed more than NKCC1, and upon binding of GABA to GABA$_A$Rs, there is an influx of Cl$^-$ into the cell, which results in hyperpolarization [33] (**Figure 2A**). When the intracellular Cl$^-$ concentration exceeds the extracellular concentration, the binding of GABA to the GABA$_A$Rs results in an efflux of Cl$^-$ from the cell, causing the membrane potential to become more positive, resulting in depolarization [34] (**Figure 2B**). This unique ability of

GABA$_A$Rs can also be observed in immature neurons during early postnatal development [35]. While both the α and β subunits can co-assemble with all other GABA$_A$R subunits, the γ and δ subunits cannot coexist within the same receptor subtype [36]. Furthermore, only the ρ1, β3, α, and γ subunits can form homo-oligomeric receptors [37]. GABA$_A$Rs vary in their affinity for GABA, expression sites (synaptic or extrasynaptic), and biophysical and pharmacological properties based on their subunit composition. For example, α subtypes have functional variation; α1 results in sedation, whereas α2 and α3 are instrumental in anxiolysis [38]. However, the expression of these subunits is dependent on the other subunits that they co-assemble within the receptor. For instance, the α(1/2/3/5)$^+$/γ2$^-$ interface is essential for benzodiazepine-mediated sedation, anxiolysis, seizure suppression, and muscle relaxation [38], and only the placement of the α subunit next to the γ subunit (α$^+$/γ2$^-$) can mediate its function. If both subunits exist within the same receptor but not in the correct order, the resulting GABA$_A$R will not be receptive to benzodiazepine. Importantly, not all potential subunit combinations can result in functional GABA$_A$Rs. Alterations in receptor composition, such as the switch from a γ2 to a δ subunit could desensitize GABA$_A$Rs to drugs such as benzodiazepines [39]. Several conditions, such as epilepsy [40, 41], traumatic brain injury [42, 43], mental illnesses (such as schizophrenia and mood disorders) [44, 45], addiction [46, 47], Alzheimer's disease [48, 49], and Parkinson's disease [50, 51], can result in alterations in the subunit composition of GABA$_A$Rs, thus highlighting the critical function of subunit configuration in healthy individuals. For more in-depth understanding of the GABA$_A$R structure and their ligand-binding site interactions, readers can refer to [30, 52, 53].
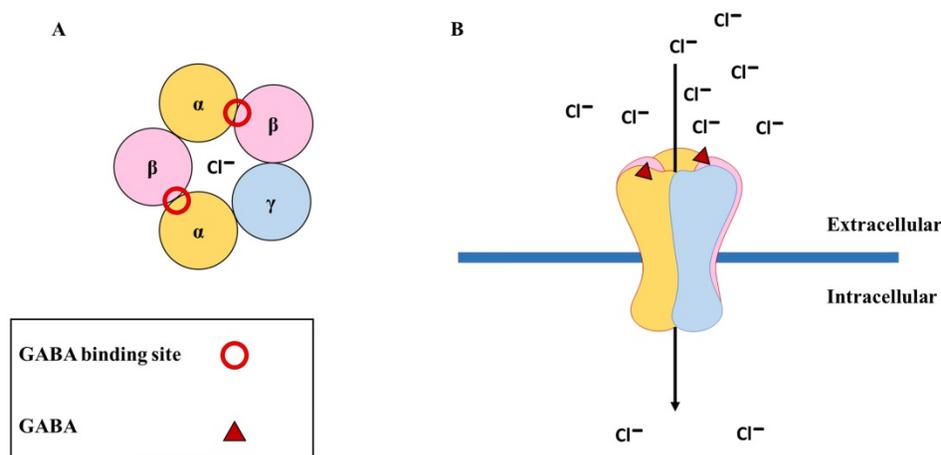

Figure 1. The physiological function of GABA$_A$ receptors. (**A**) The most common subunit configuration of GABA$_A$ receptors along with the binding sites for GABA (shown with red circle); (**B**) The binding of GABA (shown with red triangle) results in the opening of the channel, causing an influx of chloride ions (Cl$^-$) into the cell.
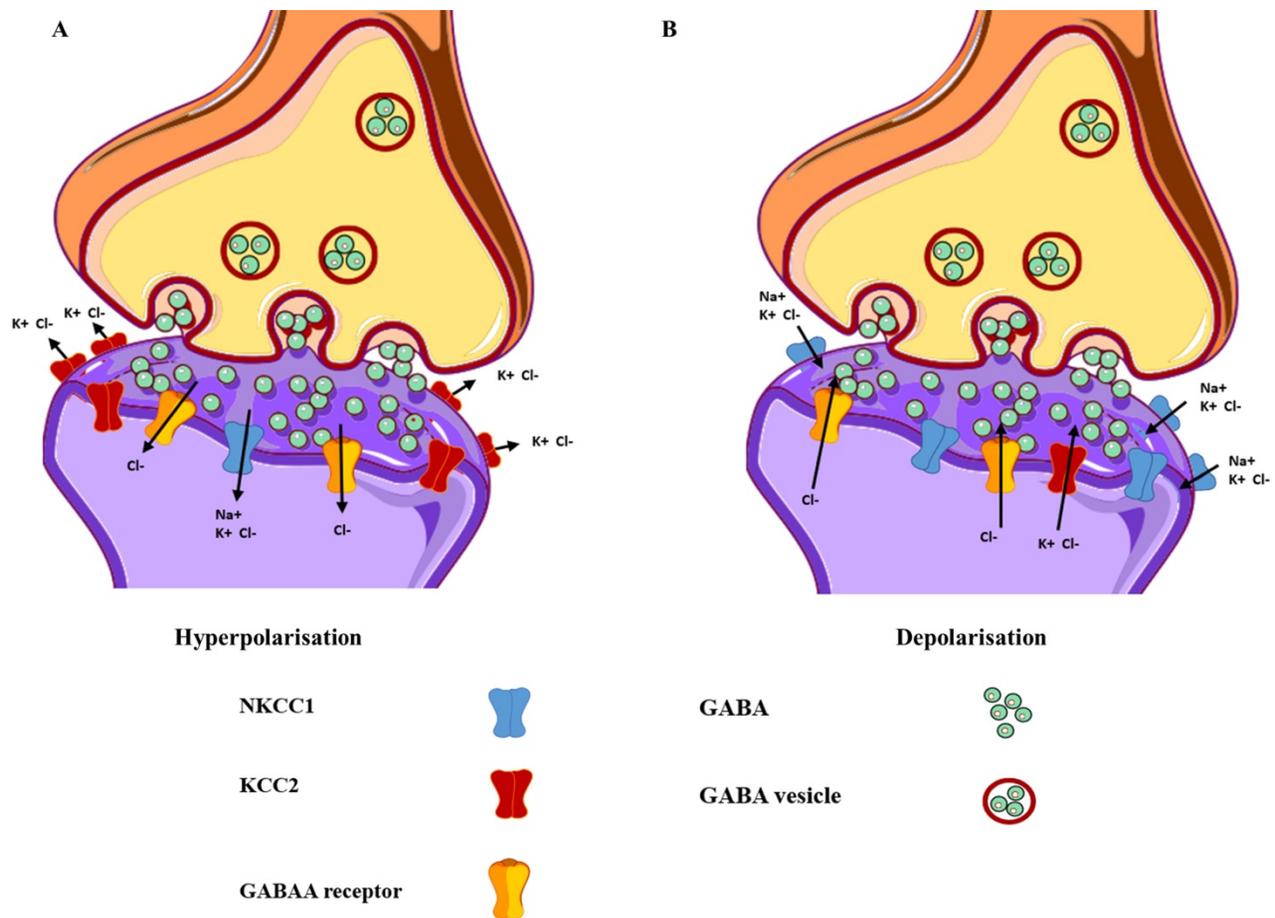
Figure 2. Differences in the functional and expressional levels of NKCC1 and KCC2. (A) Mature neurons exhibit lower expression levels of NKCC1, as compared to KCC2, resulting in hyperpolarisation. **(B)** Immature neurons express higher levels of NKCC1 in contrast to KCC2, resulting in depolarisation. The yellow structure represents the GABA$_A$ receptors, with the green circles representing the neurotransmitter GABA.

GABRP

Overview

Although GABRP was first discovered more than 20 years ago, there is not much information currently known about this receptor which possesses atypical functional properties. In comparison to other GABA$_A$R subunits, the π subunit is closely related to the β (37%), δ (35%), and ρ (33%) subunits. Previous studies have shown that the π subunit is incapable of forming homo-oligomeric receptors [54]. However, it can be co-assembled with α, β, and γ subunits to create αβπ and αβγπ isoforms [55]. GABRP exhibits differential pharmacological properties as compared to other similar GABA$_A$R isoforms (αβγ, αβδ, and αβε), increased sensitivity to inhibition by zinc ions, no sensitivity to diazepam action, and distinctive neurosteroidal regulation [55]. Located on chromosome 5q34, this receptor is expressed in several non-neuronal regions such as the uterus [56], placenta [57], pancreas [29], gastrointestinal tract [58], lungs [59], kidney [60], immune cells [61], and mammary glands [62].

Female reproductive system

In the uterus, GABRP can alter uterine motility by modulating tissue contractility [54]. Its expression levels change throughout pregnancy, with consistent levels throughout gestation followed by a reduction during the onset of labor [63]. This change in expression can modify the sensitivity of recombinant receptors to pregnanolone and allopregnanolone [54,63]. During gestation, allopregnanolone increases the binding of the GABA$_A$R agonist, muscimol, to uterine GABA$_A$Rs; in contrast, labor is marked by a limitation in this interaction, which can be attributed to the lower expression levels of GABRP [63]. Endometrial levels of GABRP also change during the secretory phase of the uterus, and elevated levels play a crucial role in acquiring endometrial receptivity for embryo implantation [56]. Similarly, a recent study found constant placental expression levels of GABRP during gestation, followed by a reduction during labor onset and a complete absence at term [64]. This suggests that GABRP has invasive potential and is involved in the development of villous trophoblasts and syncytiotrophoblasts during the first trimester,

thus ensuring a secure uterine wall implantation. GABRP can also modulate both anti-apoptotic (B-cell lymphoma 2 [Bcl-2]) and pro-apoptotic (Bcl-2-associated agonist of cell death [Bad] and Bcl-2-like protein 4 [Bax]) protein levels, and elevated placental GABRP levels are implicated in preeclampsia [57], thereby highlighting the pivotal role it plays in the female reproductive system.

Gastrointestinal tract

In the gastrointestinal tract, GABRP regulates electrolyte transport, with GABA administration resulting in increased intestinal secretion in a dose-dependent manner [58]. Increased expression of these receptors has been reported in cases of allergic diarrhea and ulcerative colitis, and treatment with a suitable $GABA_AR$ antagonist results in alleviation of symptoms [58, 65].

Lungs

GABRP also plays a role in fetal lung development by governing cell proliferation and/or fluid secretion. During gestation, elevated expression levels of α1, β2, and π subunits have been observed in fetal lung tissue from the initial stage to the later adult stages [59]. In one study, fetuses exposed to GABA exhibited a significant increase in body and lung weight with a 30% increase in the total number of saccules, a common marker for lung maturity, as compared to that in a control group. Exposure to GABA also amplified the number of alveolar epithelial type II cells while reducing the amount of α-smooth muscle actin-positive myofibroblasts [59], which indicate conditions such as asthma when present in large numbers [66]. Therefore, a reduction in this cell type suggests healthy lung development via GABRP. In another study, epithelial cells exposed to GABA also demonstrated higher Ki-67 levels [59]; Ki-67 is another marker for cellular proliferation and the development of healthy lungs, which is absent in resting cells [67]. Additionally, GABA regulates Cl⁻ efflux and resolves pulmonary oedema [68]. Notably, *GABRP*-knockout studies have reported inhibition of this efflux function [69], further supporting the critical role of GABRP in fetal lung development.

Kidneys

GABRP has also been detected at both the mRNA and protein levels in human and rat kidneys and may have an autocrine/paracrine mechanism for local GABAergic transmissions [60]. Although the receptor composition for GABRP is still debatable due to lack of consistent results from transfection studies, it has been suggested that GABRP in the kidneys is composed of a combination of α1β3π [60].

Breast

Although several studies have detected the presence of glutamic acid decarboxylase (GAD; the enzyme that synthesizes GABA), GABA [70], and significant expression levels of GABRP in healthy breast tissue, their function remain largely unknown.
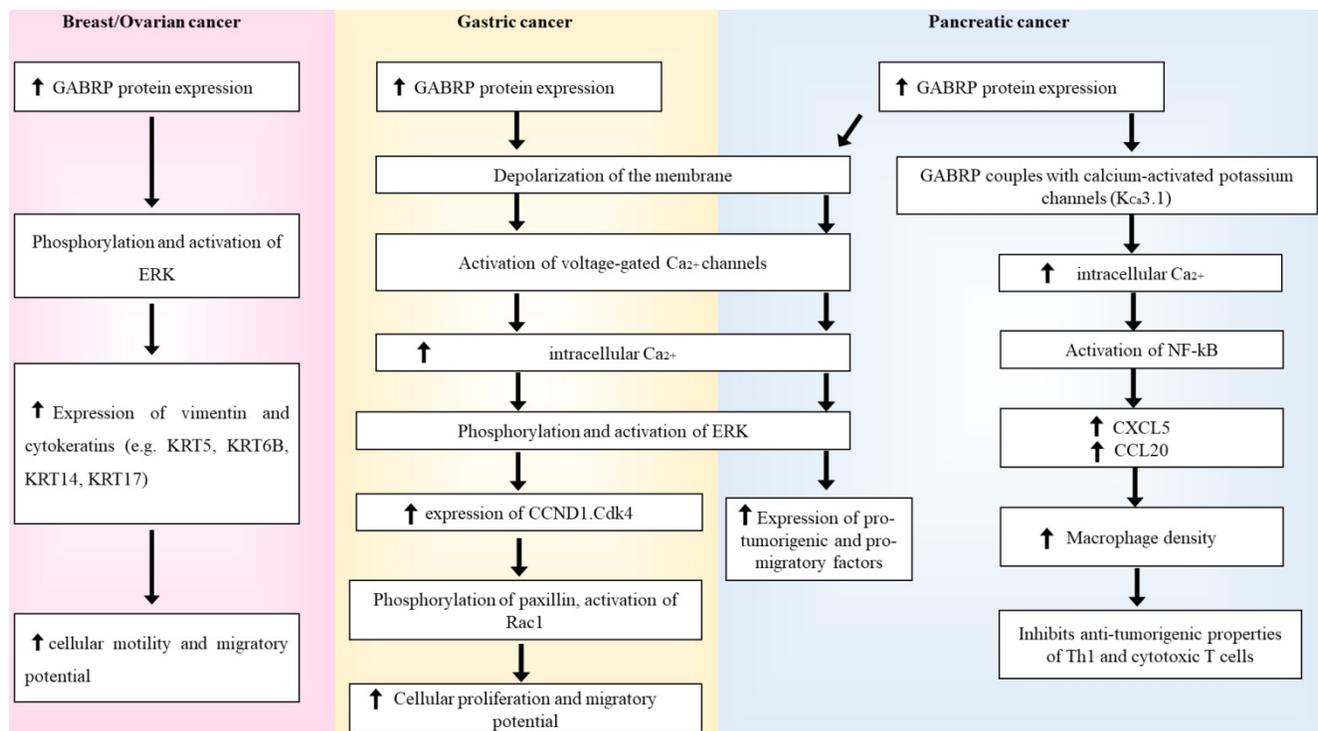

Figure 3. Summary diagram of how GABRP's regulation of ERK in breast/ovarian, gastric and pancreatic cancers.

Aberrant GABRP regulation in different types of cancer

Breast cancer

GABRP expression levels are an important indicator of the risk of recurrence of breast cancer and mortality [62]. Almost 50% of all breast cancer types exhibit high GABRP expression levels [71]. Elevated levels of GABRP have been previously reported in circulating breast cancer cells [72,73,74] and isolated lymph nodes from patients with breast cancer [75]. A multigene real-time reverse transcription polymerase chain reaction (RT-PCR) study observed patients with metastatic breast cancer expressing eight times as much GABRP as compared to stages II–IV patients with no evidence of metastasis [76]. This expression level was 30 times higher than that in stage I patients with no evidence of metastasis, suggesting that GABRP expression levels increase with disease progression and metastasis. This elevated expression level of GABRP was also effective in detecting circulating tumor cells in patients with stage I (65%), stages II–IV with no evidence of metastasis (72%), and metastatic (88.5%) breast cancer. Circulating tumor cells serve as an important indicator of the overall survival rate of patients with breast cancer [77]. Detection of GABRP expression levels can therefore prove beneficial in tracking disease progression, for instance, when traditional serum markers fail. In one study, most of the healthy controls (51 out of 53) showed low expression levels of GABRP compared to patients with breast cancer [76], and of the 2 remaining controls that exhibited high GABRP levels, 1 participant was pregnant (first trimester). The elevated expression levels of GABRP can be explained by its known physiological role in the female reproductive system. Similarly, *in vitro* studies in basal-like breast cancer (BLBC) cell lines (HCC1187 and HCC70) have also reported elevated expression levels of GABRP [78]. Other studies in healthy individuals showed that luminal progenitor breast cells also express high levels of GABRP [79]. These cells have been suggested to generate BLBC cells during carcinogenesis, further suggesting a strong connection between GABRP and the BLBC subtype [80]. Patients with BLBC often develop secondary cancer in visceral organs such as the lung, liver, and brain when the cancer metastasizes [81,82,83].

Sizemore and colleagues found a strong correlation between GABRP and the formation, migration, and aggressiveness of secondary cancer cells, thus implicating GABRP in brain metastases and poor prognosis. Lentiviral knockdown of *GABRP* in these BLBC cell lines resulted in cytoskeletal alterations, lower expression levels of basal-like cytokeratins (KRT5, KRT6B, KRT14, and KRT17), and reduced phosphorylation of the extracellular signal-regulated kinase (ERK) 1/2 signaling pathway [78]. Cytokeratins are structural proteins that form a major component of the intermediate filaments. Since their expression levels vary depending on cell types and their degree of differentiation, cytokeratins serve as suitable markers for differentiating carcinomas from other subtypes of cancer [84]. Previous studies have linked GABRP with KRT5, KRT6B, KRT14, and KRT17 in breast cancer pathogenesis [85], as several cytokeratins have been implicated in cancer cell migration [86,87,88]. Additionally, cell lines generated with functional GABRP but inhibited ERK 1/2 activity resulted in a lack of this migratory disease phenotype, suggesting that GABRP utilizes the ERK 1/2 signaling pathway to mediate its pro-migratory effects [78]. ERK 1/2 is a member of the mitogen-activated protein kinase (MAPK) family and has a highly regulated pathway that plays a crucial role in cell proliferation, differentiation, and stress response. The entire signaling pathway utilizes various kinases, such as Ras/Raf/MAPK-ERK (MEK), ribosomal s6 kinases, MAP kinase-interacting serine/threonine-protein kinases, mitogen- and stress-activated protein kinases, and cytosolic phospholipase A2 [89]. This pathway is a known modulator of bispecific phosphatases [90,91], subcellular localization of cascade components [92,93], cellular motility [94,95], cytokeratins [78,96,97,98], and other scaffolding proteins [99,100]. The ERK 1/2 signaling pathway has been implicated in several cancer subtypes [89,101,102]; therefore, abnormal manipulation of this pathway by GABRP can result in carcinogenesis. Triple-negative breast cancer (TNBC) cells have also been reported to primarily express GABRP mRNA and proteins [71]. Unlike other types of breast cancer, TNBC cells lack conventional biomarkers such as the oestrogen, progesterone, and human epidermal growth factor receptors and have also been linked to higher rates of relapse and mortality due to its aggressive nature. Therefore, the detection of GABRP mRNA and proteins in these cells could act as potential biomarkers while also providing a site for targeted therapy [103]. *In vitro* studies have shown that *GABRP* knockdown inhibits the proliferation of TNBC, whereas *GABRP* silencing suppresses the development of MDA-MB-468 xenografts in nude mice. Moreover, application of anti-GABRP antibodies or *de novo* generated Fabs in TNBC cell lines arrests further cancerous growth. When used in combination with mertansine, similar antineoplastic properties were also observed at nanomolar

concentrations [71], further underlining the prospective role of GABRP as a therapeutic target in breast cancer.

Ovarian cancer

An *in vivo* ovarian cancer study detected a >2-fold increase in the transcriptional expression levels of GABRP in metastatic implants of human ovarian carcinoma xenografts in mice compared to SK-OV-3 ovarian carcinoma cells [104]. Another study conducted by the same group found a >4-fold increase in GABRP expression levels in the metastatic tissue of the mice model [28]. Utilizing the SK-OV-3 ovarian carcinoma cell lines, several gain-of-function and loss-of-function studies were performed to analyze the role of GABRP in cellular migration and invasion. It was revealed that *GABRP* silencing reduced the invasive and migratory potential of SK-OV-3 cells while downregulating the ERK pathway. Similarly, increased expression of GABRP enhanced cellular invasion and migration and upregulated the ERK pathway. The involvement of GABRP in ERK regulation was further highlighted when the administration of U0126, a MAPK/MEK inhibitor, eliminated the invasive and pro-migratory abilities of SK-OV-3 cells, suggesting that GABRP modulates the MAPK/ERK pathway to enhance the metastatic potential of ovarian cancer [28]. Furthermore, a genome-wide DNA methylation profiling study in mouse models detected hypomethylation at the GABRP-963 CpG site. Similar results were also observed in patients who were in the advanced stages of ovarian cancer, implying that the transcriptional regulation of GABRP is governed by a DNA methylation-dependent epigenetic mechanism which further ameliorates the aggressive phenotype of ovarian cancer [28].

Cervical cancer

Cervical cancer studies have also reported higher expression levels of GABRP in metastatic tissue in patients with cancer as compared to that in controls [105]. MicroRNAs are short non-coding RNAs that affect gene silencing by targeting mRNAs at their 3-untranslated region, thus regulating protein expression levels. They are crucial for almost all cellular processes, such as differentiation, development, and homeostasis [106]. The microRNA, miR-320c, has been shown to possess anti-tumorigenic properties in cancer development as it downregulates the migratory potential of cancer cells [105]. It mediates this function by negatively regulating GABRP protein expression levels in these tissues [105]. Rescue studies have shown that patients with reduced expression levels of miR-320c had

higher protein expression levels of GABRP, thus developing lymphatic and distant metastases at a higher rate than patients with increased expression levels of miR-320c [105]. These high expression levels of GABRP were shown to reverse the effects of miR-320c and increase the migratory potential of cervical cancer cells. Additionally, the upregulation of miR-320c significantly suppressed the migratory potential of HeLa and C33-A cells due to lower expression levels of the GABRP protein. Western blotting studies have indicated that cervical cancer cells that exhibited higher expression levels of miR-320c had significantly lower protein expression levels of GABRP and lower migratory potential [105], implying a possible role for GABRP in metastatic cervical cancer.

Gastric cancer

In vitro studies in KATO III cell lines revealed GABRP-induced proliferative effects in gastric cancer [107]. RT-PCR and immunohistochemical studies confirmed that these effects are mediated through a GABA-dependent mechanism in an autocrine or paracrine manner. The integral component of this entire process is the upregulation of the ERK 1/2 pathway via GABRP, which in turn strengthens cyclin D1 expression [107]. As previously mentioned, $GABA_A$Rs have an inhibitory function (hyperpolarization) based on extracellular Cl^- levels. In cancer, there often tends to be a Cl^- imbalance that results in depolarization of the membrane, which indirectly activates voltage-gated calcium channels [108]. This raises the intracellular calcium ion (Ca^{2+}) concentration, which further activates several downstream kinases and signaling pathways. The ERK 1/2 pathway is one such cascade, which upon activation results in the transcriptional upregulation of several genes such as *CCND1* (cyclin D1), which is critical for the progression of the cell cycle from the G1 phase to the S phase [109]. Abnormal expression levels of cyclin D1 increase cancer cell proliferation, migration, and metastasis via the Ccnd1·Cdk4-paxillin-Rac1 axis [110]. Therefore, irregularities in ERK 1/2 activation due to GABRP can result in cancer. Elevated expression levels of GABRP mRNA and proteins have also been detected in oral squamous cell carcinoma cell lines [111]. Additionally, the application of muscimol or GABA further stimulates cellular proliferation, while suppressing apoptosis and arresting the cell cycle in the G2/M phase. Furthermore, when these cells were treated with the $GABA_A$R antagonist, S106, and then later re-treated with GABA, they lacked the anti-apoptotic properties that they previously exhibited, strongly supporting the pro-oncogenic nature of GABRP. The

modulation of the cell cycle was achieved via GABRP-mediated activation of the p38 pathway and downregulation of the c-Jun N-terminal kinase (JNK) signaling pathway, both of which belong to the MAPK family [111]. In healthy cells, activation of the JNK pathway results in the phosphorylation and activation of pro-apoptotic proteins such as Bcl-2-interacting mediator of cell death (BIM; homologous to BAX) and Bcl-2-modifying factor (BMF), which further activates downstream caspases. Simultaneously, JNK can also phosphorylate and inactivate anti-apoptotic proteins, such as death protein 5/harakiri, Bcl-2, and B-cell lymphoma extra-large [112]. Therefore, the downregulation of this pathway can result in uncontrolled cell proliferation and can have detrimental effects. In contrast, upregulation of the p38 pathway enhances metastasis and has been correlated with a poor prognosis in cancer [113,114,115].

Pancreatic cancer

Higher expression levels of GABRP have been observed in all grades of pancreatic ductal adenocarcinoma (PDAC) than in healthy control pancreatic tissues, implying that GABRP plays a critical role in the early stages of pancreatic carcinogenesis [29,116,117]. Small interfering RNA-mediated *GABRP* knockdown in PDAC cells was shown to significantly reduce cancer cell proliferation [117]. Additionally, the introduction of GABA to these cell lines further increased the growth of GABRP-expressing PDAC cells. However, this was not observed for GABRP-negative cells, implying that GABRP and not any other subtype of $GABA_A$Rs are responsible for the tumorigenic phenotype of the PDAC cells. Treatment of GABRP-positive cells with the $GABA_A$R inhibitor, picrotoxin, and the calcium channel blocker, nifedipine, restricted cellular proliferation. Moreover, treatment with GABA also increased the intracellular Ca^{2+} levels, which resulted in the activation of the ERK signaling pathway, and picrotoxin or nifedipine could inhibit this activation. Although $GABA_A$ receptors cause hyperpolarization in mature neurons, they have been shown to mediate depolarization in immature neurons and glial tumour cells. This activates the voltage gated Ca^{2+} channels causing an increase in intracellular Ca^{2+} levels which results in the phosphorylation and activation of the MAPK/ERK pathway [117]. Tissues derived from patients with PDAC have higher levels of GABA due to increased expression levels of GAD1, indicating an autocrine or paracrine-mediated modulation of GABRP in PDAC [117]. As previously discussed, aberrant activation of the ERK pathway results in the phosphorylation and activation of several

downstream kinases and transcription factors that are essential for cell proliferation, migration, and survival, thus supporting cancerous growth. Another recent study also suggested GABRP-mediated carcinogenesis in PDAC, but in a GABA-independent manner [29]. Macrophages are important immune cells that protect the body against harmful microorganisms via phagocytosis, while also serving other essential regulatory and repair functions [119]. Moreover, these cells possess the ability to inhibit Th1 cells and the anti-tumor abilities of cytotoxic T lymphocytes, contribute to matrix remodeling, and promote tumor cell invasion and migration [120,121,122]. GABRP can govern macrophage infiltration in PDAC cells by coupling with a calcium-activated potassium channel ($K_{Ca}3.1$), which causes an influx of Ca^{2+} and activates the nuclear factor κB. Consequently, this accelerates the expression levels of *CXCL5* and *CCL20* [29], which are known macrophage-recruiting chemokines [123]. This results in increased macrophage density which has often been correlated with a poor prognosis in cancer [118]. Pharmacological deletion of macrophages by liposomal clodronate greatly reduced the cancer proliferation of GABRP in PDAC cells [29]. *GABRP* knockdown reduced the expression levels of chemokines [29], thereby suggesting a unique immunomodulatory role for GABRP in PDAC.

Conclusion

Although this review summarizes our current knowledge of the GABRP and its enigmatic role in cancer, there are still several areas that require thorough research. A critical component requiring further investigation is its subunit composition, since there is an almost negligible amount of data currently available. Unlike its famous counterparts, the GABRP subunit composition remains shrouded in mystery. GABRP is expressed in several organs and has a few known physiological roles. These recently discovered roles in various cancer subtypes will hopefully direct more attention to these receptors. Although several studies have already highlighted the role of ERK in cancer, there are several factors that could potentially modulate this pathway; GABRP being one of them. GABRP has the potential to serve as a diagnostic marker as well as a possible therapeutic target in cancer. However, further research is needed to better understand these receptors and utilize them as potential targets in cancer therapy.

Abbreviations

Bcl-2: B-cell lymphoma 2; Bad: Bcl-2-associated agonist of cell death; Bax: Bcl-2-like protein 4; BIM: BCL-2-interacting mediator of cell death; BMF:

Bcl-2-modifying factor; BLBC: basal-like breast cancer; ERK: extracellular signal-regulated kinase; GABA: γ-aminobutyric acid; GABAARs: γ-aminobutyric acid type A receptors; GABRP: GABA receptor π subunit; JNK: c-Jun N-terminal kinase; KCC2: potassium-chloride cotransporter isoform 2; MAPK: mitogen-activated protein kinase; NKCC1: sodium-potassium-chloride cotransporter isoform 1; PDAC: pancreatic ductal adenocarcinoma; RT-PCR: real-time reverse transcription polymerase chain reaction; TNBC: Triple-negative breast cancer.

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Availability of data and material

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

Authors' contributions

- Iman Imtiyaz Ahmed Juvale: Designing and drafting the manuscript;
- Zurina Hassan: Revising the manuscript;
- Ahmad Tarmizi Che Has: Revising the manuscript critically and approving the manuscript to be published.

Competing Interests

The authors have declared that no competing interest exists.

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