Minireview

Therapeutically leveraging $GABA_A$ receptors in cancer

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Impact statement

GABA is a neurotransmitter and an amino acid with critical roles in neurotransmission and cell signaling. As a ligand for several receptors, it exerts effects that contribute to cellular differentiation, stem cell and organ development, and neural firing. This mini-review focuses on what is known concerning the presence and function of GABA with respect to Type-A GABA receptors in disparate cancers and the potential of this receptor to be leveraged therapeutically in cancer.

Abstract

γ-aminobutyric acid or GABA is an amino acid that functionally acts as a neurotransmitter and is critical to neurotransmission. GABA is also a metabolite in the Krebs cycle. It is therefore unsurprising that GABA and its receptors are also present outside of the central nervous system, including in immune cells. This observation suggests that GABAergic signaling impacts events beyond brain function and possibly human health beyond neurological disorders. Indeed, GABA receptor subunits are expressed in pathological disease states, including in disparate cancers. The role that GABA and its receptors may play in cancer development and progression remains unclear. If, however, those cancers have functional GABA receptors that participate in GABAergic signaling, it raises an important question whether these signaling pathways might be targetable for therapeutic benefit. Herein we summarize the effects of modulating Type-A GABA receptor signaling in various cancers and highlight how Type-A GABA receptors could emerge as a novel therapeutic target in cancer.

Keywords: GABA, $GABA_A$ receptors, ion channels, cancer, benzodiazepines

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Introduction

GABA was first described in 1950 as an amine present in high concentration in the brain that is synthesized from glutamic acid and biochemically differs from other amines.[1] This discovery was soon followed by the observation that GABA could inhibit the firing of neuronal action potentials. Subsequently, GABA was recognized to be a ligand that exerts its effects by binding to its cognate receptors, which were also identified.[2] We now recognize that GABA functions as a ligand that modulates the activity of at least two distinct classes of receptors: the Type-A GABA receptors ($GABA_ARs$), which are chloride anion channels; and the Type-B GABA receptors, which are metabotropic G-protein-coupled receptors. Recently, GABA has also been reported to modulate a voltage-gated potassium channel.[3]

GABAergic signaling (i.e. GABA and its interplay with its receptors) contributes to the development of the central nervous system (CNS). A nerve cell synapse is either inhibitory or excitatory, as a consequence of the neurotransmitter type that is released. The neurotransmitter glutamate, for example, functions as the principal excitatory neurotransmitter and exerts its function as a ligand that modulates at least three types of glutamate receptors (NMDA, kainate, and AMPA). The neurotransmitter GABA, on the other hand, is the primary inhibitory neurotransmitter, at least in adults. The balance between GABA's GABAergic inhibitory activity and glutamate's glutamatergic excitatory activity regulates the excitability of a nerve cell and its output. Homeostasis is necessary to prevent neuronal dysfunction and disease. Such dysfunction has been implicated in varied CNS disease states, including pathogenesis of anoxic-ischemic injury and epilepsy.[4] GABA signaling is also associated with the inflammatory response following traumatic brain injury and contributes to the neuronal effects of stroke.[4]

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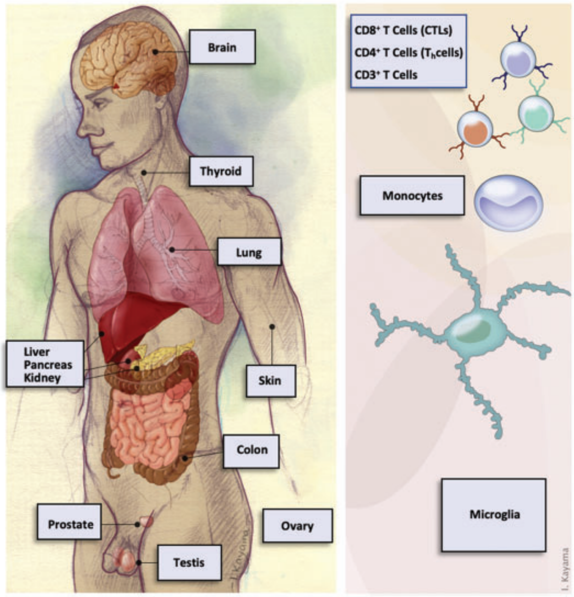

Figure 1. Expression of Type-A GABA receptor subunit genes in normal human tissues. Genes coding for subunits of Type-A GABA receptor, *GABR* genes, has been observed in the CNS and from many systemic sources (left). Expression of *GABR* genes has also been reported in various cells of the immune system (right). In many of these tissues and cells, Type-A GABA receptor activity has been reported and connected to function.

Importantly, GABA and its varied receptors are found not only in the CNS but throughout the body, including immune cells. Figure 1 illustrates the presence of GABA$_A$Rs in many human cell types. This ubiquity suggests that the role of GABA and its varied receptors may be far greater than the regulation of firing of action potentials in neurons. Indeed, GABA receptor function has been linked to several critical roles outside the CNS. One of the more studied roles is its contribution to pancreatic function.[5] GABA is synthesized with insulin in the beta-cells of pancreatic islets, while the glucagon-producing alpha-cells contain GABA$_A$Rs. The fascinating interplay that has evolved between GABA secretion from beta-cells and its binding to GABA$_A$R in alpha-cells acts to regulate glucagon levels. In addition, GABA signaling may contribute to tumorigenesis within the CNS and in systemic organs, potentially mediating crosstalk between normal and cancer tissue to create an ameliorated microenvironment for the tumor and/or drive metabolic processes resulting in growth of cancer.[6–9] The expression of GABA and its receptors combined with their possible functions in disparate cancers suggest that they might be therapeutically beneficial targets for the treatment of cancers.

GABA$_A$R structure

At least 19 genes code for different GABA$_A$R subunits.[10,11] The complexity of possible GABA$_A$Rs that may be formed from such a repertoire of genes is further expanded by alternative splicing, use of alternative promoters, and post-translational modification of subunits. At baseline, *GABR* genes contribute to the assembly of a ligand-gated pentameric chloride anion channel, the GABA$_A$R. Most commonly, GABA$_A$Rs are composed of two α, two β, and a γ-subunit encoded by *GABR* genes *GABRA* (1 to 6), *GABRB* (1 to 3), and *GABRG* (1 to 3), respectively.[12] Its five subunits assemble around a central transmembrane hole that forms the chloride anion conduction pore (Figure 2(a)). Structurally, all GABA$_A$R subunits form a similar topology.[12] The two binding sites for the receptor's endogenous ligand GABA are created at the interface between the α- and β-subunits.

GABA$_A$R function in the developing and mature central nervous system

GABA itself is released from pre-synaptic neurons and binds to GABA$_A$Rs, which are primarily embedded in the post-synaptic neuronal membrane. The binding of GABA to GABA$_A$R acts to promote a chloride anion flux into post-synaptic cells leading to hyperpolarization (Figure 2(b)). This well-studied phenomenon has been a major pharmacologic target since the introduction of the benzodiazepines diazepam (Valium) and chlordiazepoxide (Librium) nearly 70 years ago, which function as positive allosteric modulators, acting to enhance the chloride anion flux through GABA$_A$Rs in the presence of GABA[12] (Figure 2(b)). What remains less well understood is the role of GABA and GABA$_A$R in the developing neuron and brain structures, their role(s) outside of the central nervous system, and their contribution to brain and systemic pathologies, including cancers.

In the developing brain, the effect of GABA is depolarizing, not hyperpolarizing, and it acts as a principal excitatory, not inhibitory, neurotransmitter.[13] GABA stimulation in immature neurons functions to trigger an efflux of chloride anions, mediated by the triggering of sodium spikes and activating voltage-gated Ca^{2+} channels. Through this process, GABA acts as a trophic factor during neuronal development and influences cellular events including proliferation, migration, differentiation, synapse maturation, and cell death.[14,15] Shortly after birth, a chemical change occurs, historically referred to as the "GABA switch", which is crucial for neuronal development and activation of neuronal cells. In pre-natal neuronal development, chloride levels are strictly regulated within a range of 15–20 mM, whereas within the first week after birth, the resting chloride concentration drops to 4 mM.[16] The GABA response shifts from excitatory to inhibitory in neurons driven by these changes in intracellular chloride concentrations. Functionally, the equilibrium potential $[Cl^-]_i$ in neurons shifts from −46 mV at birth to −82 mV at postnatal day 10, which is very close to the depolarization threshold.[17] Ca^{2+} imaging studies in rodents show that commensurate with this change, activation by GABA results in the accumulation of an intracellular concentration of Ca^{2+} that is required for downstream signaling, resulting in increased expression of membrane transporters.[13] In immature neurons, the Na^+-K^+-$2Cl^-$ (NKCC1) co-transporter is expressed in the early stages of development and is responsible for the elevated $[Cl^-]_i$ concentration. The chloride exporter K^+-Cl^- cotransporter (KCC2), which maintains lower $[Cl]_i$, has delayed expression[17] and thus a major

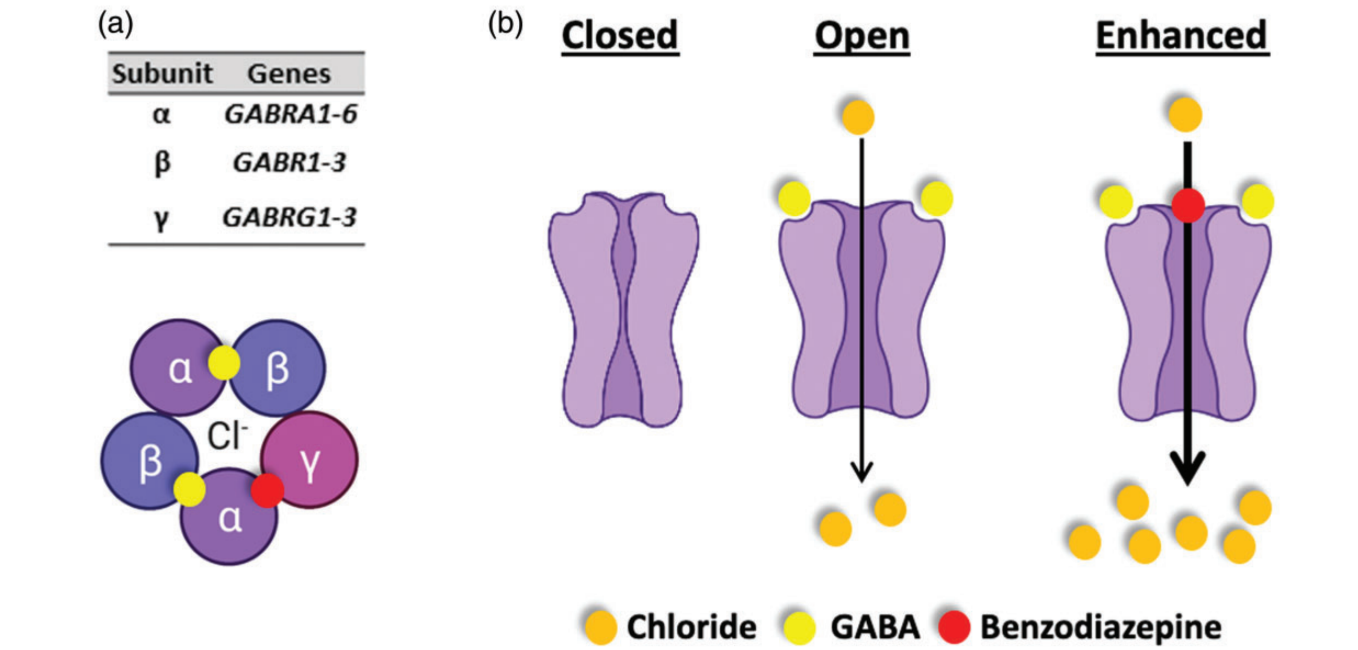

Figure 2. Type-A GABA receptor function-structure. (a) Type-A GABA receptor is a pentameric assembly with five transmembrane subunits that form a ligand-gated ion channel. Shown are binding sites for two GABA ligands (yellow spheres) and benzodiazepine (red sphere). (b) Type-A GABA receptors function to move chloride anions across the cell membrane in response to the binding of its ligand (agonist) GABA. Benzodiazepines are positive allosteric modulators of the receptors and so act to enhance movement of chloride anions when GABA is bound to the receptor.

role in the GABA switch from excitatory to inhibitory.[16] The effects of postsynaptic currents are mediated by Ca^{2+} influx, which leads to an increased KCC2 signal. This signal is described as a new form of $GABA_AR$ feedback, resulting in the GABA switch.[18–20]

GABA and $GABA_AR$ function beyond the central nervous system

GABA is present throughout the body and expression of $GABA_AR$ subunits has been observed in diverse tissues, including lung,[21] pancreas,[5,22,23] kidney,[24] intestine,[25] prostate,[26] testis,[10,27] ovary,[10,28] liver,[29] thyroid,[30] and skin (melanocytes)[31] (Figure 1). Several studies have highlighted the importance of GABA signaling to cell proliferation, migration, and differentiation.[32–34] Still, the importance of GABA and $GABA_AR$ to cell signaling beyond synapses remains largely unexplored. Two potentially important roles of GABA and $GABA_AR$ that may be linked to their importance in cancer are within the immune system and stem cell development.

GABA and $GABA_AR$ appear to contribute to the development and functioning of the mammalian immune system. Nucleated immune cells that express subunits of $GABA_AR$s include all the white blood cell types, lymphocytes of the CD4+ and CD8+ T cell lineages, neutrophils, and macrophages.[35–37] Antigen-presenting cells (APCs) and T cells both secrete endogenous GABA and possess functional $GABA_AR$s (e.g. the receptors exhibit a current in response to GABA).[38] It is important to note that GABA has been reported to function as an immunomodulator with an ability to either activate or suppress cytokine secretion, modulate T cell proliferation, and alter the migration of T cells.[39] $GABA_AR$ in CD3+ T cells, for example, can regulate T cell responses in inflammation. Moreover, pharmacologic agents that modulate GABAergic signaling can stimulate $GABA_AR$s present on APCs and macrophages.[40,41] For example, blocking $GABA_AR$ function prevents pressure-induced macrophage phagocytosis, suggesting that $GABA_AR$ plays a role in this process.[40] Studies have also shown that functional $GABA_AR$s are present on monocytes, and anesthetics like propofol and thiopental impair monocyte function by directly acting on $GABA_AR$.[40] Blocking $GABA_AR$ reverses the inhibition of monocyte migration and phagocytosis induced by anesthetics.[42]

Stem cell renewal requires proliferation under sustained maintenance of multipotency. GABA signaling (autocrine or paracrine) through $GABA_AR$ inhibits proliferation of embryonic stem (ES) cells and peripheral neural crest stem (NCS) cells and attenuates pre-implantation embryonic growth and proliferation in the stem cell niche.[43] Activation of $GABA_AR$ triggers accumulation of stem cells in the S phase, leading to a rapid reduction in cell proliferation. Inhibition of endogenous signaling by the $GABA_AR$ antagonist bicuculline or siRNA-mediated knockdown of $GABA_AR$ subunits in high-density ES cell cultures significantly increases proliferation of NCS cells.[43] In addition, the $GABA_AR$ agonist muscimol rapidly increases phosphorylated histone H2AX (γ-H2AX) levels in the nuclear foci of ES cells.[44] Further, Wang *et al.* reported that propofol, a $GABA_AR$ positive allosteric modulator, inhibits proliferation of rat embryonic NCS cells.[45] These observations position $GABA_AR$ as a key regulator during development via control of chromatin structure-function.

Ion channels in cancer

Ion channels, including $GABA_AR$, regulate important physiological functions such as cellular excitability, ion homeostasis, and cell migration. And as noted for $GABA_ARs$, ion channel dysfunction contributes to various disorders or channelopathies. Ion channels may also contribute to invasive tumor metastasis and tumor development and progression.[46] Rapidly proliferating cancer cells have a depolarized membrane potential as compared to non-proliferating cells, which can contribute to driving cell proliferation.[47] This was discussed further in Sengupta *et al.*,[48] whereby cancer cells expressing $GABA_ARs$ were similar electrophysiologically to $GABA_ARs$ during embryonal development. Further, ion channels orchestrate intracellular signaling such as a sustained influx of Ca^{2+} ions that trigger downstream signals essential for various intracellular processes, such as activation of transcription factors, release of cytokines, and cell proliferation.[49,50] For example, ion channels such as KCa3.2 and Orai1 can enhance the migratory ability of cancer cells, contributing to metastasis in breast and colon cancers.[46,51,52] Ion channels can also generate aberrant bioelectric signals that can initiate oncogenic processes.[53]

Tumors have developed multiple ways to escape immune surveillance. Tumor microenvironments are highly acidic in nature. Moreover, ion channels (e.g. the P2X family) in cancer cells assist in the production of chemicals such as chemokines and cellular metabolites such as adenosine that help tumors metastasize and evade immune cells.[54] The adenosine pathway is one of the most well-characterized extrinsic mechanisms of resistance to immunotherapy.[55] Adenosine is involved in reducing the function of KCa3.1 channels through the A2A receptor on peripheral blood and tumor-infiltrating CD8+ T lymphocytes (TILs), thereby disabling their migratory abilities during tumor infiltration of head and neck cancer patients.[56] Hypoxic tumor microenvironments downregulate the expression of Kv1.3 channels and reduce their function on TILs in head and neck cancer. Tumor microenvironments have an elevated K^+ concentration, which suppresses T cell function. Overexpression of the voltage-gated Kv1.3 channel and Ca^{2+}-dependent KCa3.1 channels in T cells of a mouse melanoma model has been shown to reset the ionic checkpoint by lowering the concentration of K^+ ions inside the cells and counteracting T cell suppression by elevated K^+ ions.[55]

Ion channels and their association with membrane receptors such as integrins have an intricate relationship in cancer development that has been shown to increase tumor malignancy. Several studies in neuronal and leukemic cells show that integrins are involved in differentiation, migration, and neurite extension, and this activity is mediated through ion channel activation.[57] Voltage-gated sodium channels have accessory beta subunits that are altered and detected in the early onset of tumor metastasis, highlighting the critical role of accessory subunits of ion channels in cancer development.[58,59]

Like other ion channels, $GABA_ARs$ may contribute to the development and maintenance of cancers. Genes coding for subunits of $GABA_AR$ have been reported to have roles in cancers of the central nervous system (gliomas,[60–62] medulloblastoma,[48,63–65] and neuroblastoma[66,67]) as well as systemic cancers, including of the lung,[9,68,69] breast,[70,71] pancreas,[72] liver,[73] colon,[74] prostate,[75] thyroid,[76] ovaries,[30] and skin (melanoma).[31] In many of these cancers, *GABRA3*, which codes for the α-3 subunit of $GABA_AR$, appears critical. For example, there is enhanced expression of *GABRA3* in breast cancer cells and it appears to contribute to its migration and invasive properties.[70,71] Specifically, in these cells, $GABA_AR$ containing α-3 contributes to the activation of the serine/threonine-specific protein Akt, which has a prominent role in regulating cell proliferation and migration in cancer cells. This may explain the high metastatic propensity of breast cancer cells with enhanced *GABRA3* expression.

Pomeroy and his co-workers reported in their analysis of genomic sequencing of medulloblastoma tumors from patients, an enhanced expression of *GABRA5*, which codes for the α-5 subunit of $GABA_AR$.[63] Interestingly, a more extensive analysis of *GABR* expression in the four subgroups of medulloblastoma revealed enhanced *GABRA3* in another subgroup, and within a subset of patients within another subgroup, a different, unique set of *GABR* genes were expressed[65] (Figure 3). In a study exploring the importance of *GABRA5* in medulloblastoma patients, it was found that knock-down of *GABRA5* and

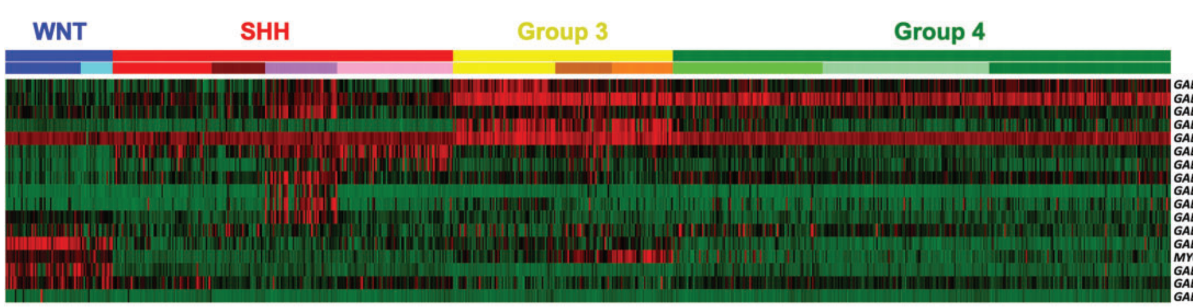

Figure 3. Expression of Type-A GABA receptor subunit genes in the pediatric brain cancer medulloblastoma. Shown is a heatmap across four molecular subgroups of medulloblastoma (Top row: WNT, SHH, Group 3, and Group 4) and subtypes within each subgroup (lower row), where color scaling indicates low (green) to high (red) expression. In Group 3 patient tumors (yellow), there is enhanced expression of *GABRA5*, which codes for the α-5 subunit. In contrast, in WNT patient tumors (blue), there is enhanced expression of a different set of *GABR* genes. While in SHH patient tumors (red) there is a subset of patients (purple) that share an enhanced expression of yet a different set of *GABR* genes. Figure adapted from Kallay, *et al.* Modulating native GABAA receptors in medulloblastoma with positive allosteric benzodiazepine-derivatives induces cell death. *J Neurooncol* 2019;142:411–422.

ostensibly $GABA_AR$ function, significantly reduced the growth of patient-derived medulloblastoma cells. This suggested that $GABA_AR$ contributed to the growth of this cancer.[48] It remains to be determined whether the other subgroup-specific set of *GABR* genes are important in the development of these different medulloblastoma subgroups.

In addition to *GABRA3* and *GABRA5*, enhanced expression in breast cancer cells of the $GABA_AR$ subunit pi, encoded for by *GABRP*, has been reported. This subunit is incorporated in place of the gamma to form a pentameric channel with an alpha2-beta2-pi1 stoichiometry. In basal-like breast cancer (or BLB-C subtype), *GABRP* expression is enhanced,[70] appears associated with metastases to the brain, and correlated with poorer prognosis in patients. Mechanistically, $GABA_AR$ containing the subunit pi appears to also play a role in maintaining basal-like cytokeratin expression and ERK1/2 phosphorylation and activation, both of which sustain the pro-migratory phenotype of BLB-C subtype cells. This may explain the intrinsic aggressive behavior of BLB-C and the enhanced propensity of visceral metastasis, including to the CNS. Enhanced expression of *GABRP* has also been noted in pancreatic ductal adenocarcinoma and GABA is reported to stimulate cell proliferation.[72] This phenomenon appears mechanistically to be triggered by activation of the MAPK/ERK pathway, which also contributes to the maintenance of the tumor phenotype and possibly metastasis to the CNS.[72]

$GABA_AR$ as a therapeutic target in cancer

If GABAergic signaling contributes to the development and/or growth of cancer cells, might it be possible to perturb tumor formation and/or cancer proliferation by disrupting GABAergic signaling? A clinical report from over 35 years ago suggests it may. Kleinerman *et al*. conducted a retrospective analysis of breast cancer patients and benzodiazepine usage, reporting that use of the benzodiazepine diazepam correlated with reduced primary tumor size and less incidence of lymph node involvement.[77] A possible explanation is that patients taking diazepam fared better because these patients sought and received an anxiolytic (e.g. a benzodiazepine) that helped them in dealing with the understandable anxiety that they were experiencing. Alternatively, the breast cancer tumor cells and/or cells in the tumor microenvironment may have been responsive to diazepam in a way that contributed to an anti-cancer effect.

Recent studies in the pediatric brain cancer medulloblastoma and in melanoma indicate that benzodiazepines have an anti-cancer effect, but how could this be? Interestingly, it was reported in a study of medulloblastoma that a series of benzodiazepine analogs that had a preference to bind to *GABRA5* containing $GABA_AR$ impaired viability of cells in culture (IC_{50} 1–0.1 micromolar) and induced apoptotic responses *in vivo*.[48,64] Strikingly, the effect *in vivo* was more significant and specific than standard-of-care chemotherapeutic.[64] Mechanistically, this phenomenon was dependent upon *TP53* expression as well as homeobox transcription factor *HOXA5*, which regulates p53 expression.[48] These results on face value seem counterintuitive, how could a pharmacologic that enhances $GABA_AR$ function impair cancer cell viability, while knock-down of $GABA_AR$ function elicit the opposite effect? In a follow-up study, exploring details of how benzodiazepines may impair medulloblastoma cells, it was shown by single-cell electrophysiology that the benzodiazepine analogs tested induced a chloride anion efflux from the medulloblastoma cells, which depolarized their mitochondria as well as induced fission[65] (Figure 4). Given that during the development of cells $GABA_AR$ is also depolarizing and NKCC1 expression is observed, a contributing role to the development of medulloblastoma may be that these cells have not

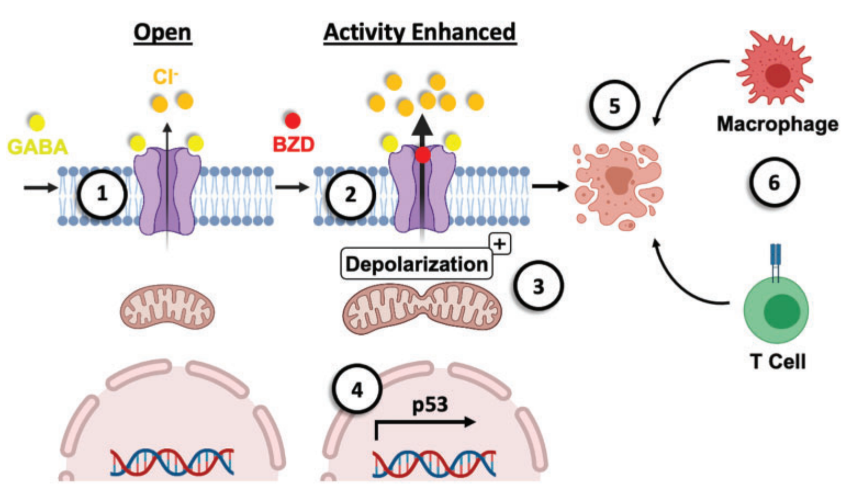

Figure 4. Model of the mechanism of benzodiazepine-mediated cell death. (1) Binding of GABA (agonist) to a Type-A GABA receptor ($GABA_AR$) "opens" the channel to allow flow of chloride anions out of a cancer cell. This efflux of chloride anions is reflective of the depolarizing nature of the $GABA_AR$ in embryonal cells. (2) Benzodiazepines (positive allosteric modulators of the receptor) enhance the chloride efflux. (3) The significant movement of chloride anions contributes to depolarizing of the mitochondria in the cancer cell and induces mitochondrial fission. This may contribute to mitochondrial dysfunction such as release of reactive oxygen and/or nitrogen, as well as impact ATP production. (4) The p53 signaling pathway is activated in these cancer cells in response to perturbation in ion homeostasis. (5) In addition, the intrinsic (mitochondrial) apoptotic pathway is triggered with an associated role for the pro-apoptotic protein BAD, BCL2 associated agonist of death. (6) In addition to binding to resident $GABA_AR$ on cancer cells, benzodiazepine binds to the $GABA_AR$ on immune cells. This event may contribute to enhanced infiltration of polyfunctional CD8+ T cells and macrophage phagocytosis.

undergone a "GABA-switch", which is reflective of the embryonal origin of medulloblastomas. In conclusion, GABA$_A$R may indeed contribute to cancer development, but when chloride anion efflux is significant as a consequence of benzodiazepine binding to GABA$_A$R, then a stress response is elicited that drives an apoptotic response via the intrinsic (mitochondrial) pathway involving the activation of the pro-apoptotic protein BAD, BCL2 associated agonist of death[48, 65] (Figure 4).

These observations in medulloblastoma are seen in other CNS and systemic cancers. In gliomas, for example, there is a correlation between the expression of certain *GABR* genes and poor prognosis.[61] While Blanchart *et al.* found that muscimol, a competitive agonist of GABA derived from the mushroom *Amanita muscaria*, can regress glioblastoma tumor growth and increase overall survival in a mouse model.[62]

Turning to systemic cancer, it was recently reported that melanoma cells possess GABA-responsive GABA$_A$Rs and benzodiazepines enhance chloride anion transport through the receptors. Importantly, the effect of the benzodiazepines on melanoma cells was similar to that on medulloblastoma cancer cells, benzodiazepines elicited a chloride efflux, which depolarized their mitochondria and induced apoptosis.[31] Interestingly, while the IC50 in culture was not significant (~1–5 micromolar), the effect *in vivo* was pronounced. The benzodiazepines mediated a significant regression in tumor size, even at a concentration equivalent to what an adult would take as an anxiolytic. The melanoma mouse model used in these studies was syngeneic and so the role of the immune system in this phenomenon could be analyzed. Interestingly, immuno-profiling of the melanoma tumors revealed enhanced infiltration of immune cells in the tumors of benzodiazepine-treated mice. This may indicate that while benzodiazepines were capable of eliciting apoptotic responses in tumor cells, also contributing to regression of the tumors were immune cells such as macrophages responding to benzodiazepines enhancing their GABA$_A$R function (Figure 4).

Is it reasonable to consider benzodiazepines as an anticancer therapeutic in cancers that have functional GABA$_A$Rs? Clinically, treating a patient with a singular drug approach does not show durable responses in many cancers. Where benzodiazepines may have the greatest impact is as a "sensitizer" of cancer cells. In medulloblastoma, benzodiazepines were capable of sensitizing cancer cells to chemotherapy or radiation.[48] This is critically important as the doses required of both treatment modalities cause cognitive deficits in children. Thus, if it were possible to both increase chemotherapeutic and radiation efficacy while reducing their toxic side-effects, this would be a victory for an "add-on" therapeutic. In the case of metastatic melanoma patients, ~50% have brain metastases and the median survival of metastatic melanoma is just seven to eight months. Treatment with radiation and immune checkpoint inhibitors is completely inadequate for metastatic melanoma, even though we are seeing positive outcomes for non-metastatic melanoma.[78] Benzodiazepines were shown in a melanoma mouse model to enhance the effectiveness of radiation, even at a sub-lethal dose, and immune checkpoint inhibitors.[31] The data appear promising for benzodiazepines as a potential sensitizer of standard-of-care for melanoma. When melanoma mice were treated with benzodiazepines in combination with radiation and an immune checkpoint inhibitor, there was a complete loss of tumors in most mice.

Conclusions

GABAergic signaling has evolved to serve multiple specialized functions; for example, nociception in the gastric tract, pancreatic beta-cell insulin secretion, and enhancing proliferation of stem cells. Interestingly, the role(s) of GABAergic signaling differ during and post-development. Unfortunately, GABAergic signaling may also contribute to the pathobiology of a wide array of disorders, including CNS and systemic cancers. We have only scratched the surface at understanding how GABAergic signaling may contribute to the development of cancers as well as contribution to the maintenance of a tumor microenvironment in the context of normal tissue. There remain many questions, one being how GABA$_A$R may mediate crosstalk in the tumor microenvironment between non-cancer cells including immune cells and the tumor cells. We have detailed studies that show that by enhancing GABAergic signaling by employing GABA$_A$R positive allosteric modulators such as benzodiazepines, tumor invasiveness, and proliferation of CNS and systemic cancers can be inhibited. In addition, activation or enhancement of GABA$_A$R activity can sensitize cancer cells to radiation, chemotherapeutic, and immune checkpoint inhibitors. A clinically available brain-penetrant anxiolytic that can function to fight cancer should be a welcomed addition to the anti-cancer arsenal.

AUTHORS' CONTRIBUTIONS

All authors contributed to the writing of the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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