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GABA's Control of Stem and Cancer Cell Proliferation in Adult Neural and Peripheral Niches

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Abstract

Aside from traditional neurotransmission and regulation of secretion, γ-amino butyric acid (GABA) through $GABA_A$ receptors negatively regulates proliferation of pluripotent and neural stem cells in embryonic and adult tissue. There has also been evidence that GABAergic signaling and its control over proliferation is not only limited to the nervous system, but is widespread through peripheral organs containing adult stem cells. GABA has emerged as a tumor signaling molecule in the periphery that controls the proliferation of tumor cells and perhaps tumor stem cells. Here, we will discuss GABA's presence as a near-universal signal that may be altered in tumor cells resulting in modified mitotic activity.

γ-Amino butyric acid (GABA) is an important amino acid and the main inhibitory neurotransmitter via activation of specific receptors highly expressed throughout the central nervous system (CNS). It has become clear that GABA has a role beyond synapses. GABA controls secretion in peripheral organs and acts as a developmental signal in both embryonic and adult developing or regenerating tissues. GABA through $GABA_A$ receptors affects every stage of cell development (i.e., proliferation, migration, and differentiation). In particular, GABA controls the proliferation of many different cell types, including stem cells. Both the brain and many of the adult peripheral organs (if not all) contain proliferative cells, including adult stem cells. The latter self-renew, generate cells of the tissue in which they reside, and are found in a special microenvironment called the stem cell niche. A tight GABAergic signaling has been found in neural stem cell niches where GABA limits the number of proliferative stem cells. Data regarding GABA signaling and function on proliferation are more scant in peripheral stem cell niches, although there is evidence that GABA can control the proliferation of certain types of peripheral cells. Nevertheless, many studies suggest that GABA and GABAergic signaling components exist in peripheral organs where putative stem cells reside (see Table 1).

Intriguingly, GABA has also emerged as a tumor signaling molecule in the brain and periphery that controls tumor cell proliferation (for review, see Refs. 161,187). In most cases, the levels of $GABA_A$ receptors or other signaling components are upregulated in cancer cells (for review, see Ref. 161). This raises the possibility that manipulating $GABA_A$ receptor activity may reduce tumor growth. For example, the $GABA_A$ receptor allosteric agonist nembutal has been shown to inhibit experimental colon cancer growth and metastasis (169). With growing evidence implicating the existence and role of cancer stem cells in tumor generation and progression, eliminating tumors may require targeting these stem/progenitor cells and

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determining whether there is altered $GABA_A$ receptor expression and function (for reviews, see Refs. [50],97,99,110,119,136,199).

Here, we first review the anatomy of the brain and peripheral stem cell niches with particular emphasis on a subset of ograns (i.e., the liver, pancreas, and prostate). We will attempt to emphasize similarities between these niches. We focused on these organs because they have known GABAergic signaling under both normal and tumor conditions. Other organs such as the testis have well described components of the GABAergic signaling (57,186), but very little is known under tumor condition. We then describe the known GABAergic components in these niches and the known function of $GABA_A$ receptor activation with regard to cell proliferation. Finally, we highlight elements of GABAergic signaling that are altered in tumors of the liver, pancreas, and prostate and may thus provide therapeutic targets for manipulating the proliferation of cancer cells and perhaps cancer stem cells.

GABA and Its Receptors: Brief Overview

GABA is synthesized primarily from glutamate by glutamate decarboxylase (GAD65 and GAD67) and is degraded by GABA-transaminase. Ambient GABA levels are tightly controlled by high-affinity sodium-dependent GABA transporters (22). GABA functions are triggered by binding of GABA to its ionotropic receptors $GABA_A$ and $GABA_C$, which are ligand-gated chloride channels, and its metabotropic receptor $GABA_B$. Our focus will be on $GABA_A$ receptors, which are heteropentamers primarily composed of α1–6, β1–3, and γ1–3 subunits (other subunits include δ, ε, π, ρ, and τ) (for review, see Ref. 74). $GABA_B$ receptors are expressed in some stem cells such as human CD34-positive hematopoietic stem and progenitor cells (156) and have been shown to control the proliferation of certain cell types such as Schwann cells, hepatocellular cells, and gastric carcinoma cells (109,166,184). However, there are fewer studies examining the function of $GABA_B$ receptors on stem cell proliferation. All the components of the GABAergic signaling listed above are highly expressed in the brain as well as in peripheral organs such as the pituitary (44,68), pancreas (islets of Langerhans) (21, 62,89,175,193), kidney (6,26,30,106,175,189), intestine (137,186), prostate (121), testis (2, 36,58), ovary (2,45), and liver (114) (for reviews or references for several organs, see Refs. 64,73,85,163,186,195) (summary in FIGURE 1).

Adult Brain and Peripheral Stem Cell Niches

Adult stem cell niches are distributed throughout the body, including the brain. Several peripheral stem cell niches have been well characterized such as the skin, bone marrow, testis, liver, and kidney (for reviews, see Refs. 52,146). Here, we focus on four stem cell niches in the body (FIGURE 2): the subventricular zone (SVZ) in the brain, the liver, the pancreas, and the prostate. We focused on these stem cell niches because components of GABAergic signaling within these central and peripheral regions have been examined under normal and tumor conditions. Table 1 summarizes the cell composition, stem cell identity, and GABAergic elements of these peripheral niches as well as references to the testis and kidney. A brief anatomical description is provided for each of these organs as well as a short discussion on the existence and identity of putative stem cells in these tissues.

Adult neural stem cell niches

In adult tissue, there are two neurogenic zones, one along the lateral side of the lateral ventricle, called the SVZ, and another one in the dentate gyrus of the hippocampus, called the subgranular zone (SGZ) (for reviews, see Refs. 23,102,197). Here, we focused on the SVZ because the GABAergic signaling and its function on cell proliferation have been studied in greater detail than in the SGZ. The SVZ-ependymal region contains at least four different cell types defined by their morphology, ultrastructure, and molecular markers FIGURE 2, A AND B) (4,5,16,

38,[84],[90],[104],131,138,151,151). Neuroblasts (referred to as type A cells or neuronal progenitors) migrate in chains along the rostral migratory stream (RMS) to the olfactory bulb, where they differentiate into interneurons (5,103,108). A particular type of protoplasmic astrocytes [also called type B cells or glial fibrillary acidic protein (GFAP)-cells here] ensheath the chains of migrating neuroblasts. Highly proliferative progenitors (transit amplifying cells or type C cells) are scattered among migrating neuroblasts. The SVZ is largely separated from the ventricular cavity by a layer of ependymal cells. Other cell types or structures include microglial cells and blood vessels (149,167).

In the adult SVZ, cells with stem cell characteristics express the glial filament GFAP (37,54, 96). SVZ cells also express a class VI intermediate filament protein nestin (38), originally identified in radial glia (75). These GFAP cells generate intermediate progenitor cells, the transit amplifying cells, which themselves asymmetrically divide and generate neuroblasts (37,135). For example, following elimination of fast-dividing cells, neuroblasts, and transit amplifying cells, with the use of cytosine-beta-D-arabinofuranoside, slow-dividing GFAP-cells were activated (i.e., proliferate) and regenerated the entire SVZ in ~2 wk in rodents (39). Finding immature cells in the SVZ expressing GFAP, which is a well known marker of mature astrocytes, was surprising because astrocytes in the adult brain were thought to be fully differentiated with their own functions (182). In addition, GFAP-cells in the SVZ have the dual function of acting as stem cells and as niche cells (commonly called “stromal cells” in peripheral stem cell niches), thus playing a neurogenesis-promoting role (14,152).

Liver

The liver contains four lobules formed by parenchymal cells, i.e., hepatocytes, and nonparenchymal cells (FIGURE 2, C AND D). Hepatocytes occupy 80% of the total liver volume and perform the majority of numerous liver functions. Nonparenchymal liver cells occupy only 6.5% of the liver volume but contribute to 40% of the total cell number. Nonparenchymal liver cells are localized in the sinusoidal compartment of the tissue (i.e., in the walls of hepatic, sinusoidal blood vessels) and are divided into three different cell types: sinusoidal endothelial cells, Kupffer cells (specialized macrophages), and hepatic stellate cells (HSCs, formerly known as fat-storing cells, Ito cells, lipocytes, and perisinusoidal cells). The stellate cells are thought to serve as liver support and repair after liver insults and act as liver “niche” cells (141, 145).

The liver is well known to be capable of natural regeneration of lost tissue. This is predominantly due to the hepatocytes re-entering the cell cycle. However, there is also strong evidence of bipotential stem cells, called ovalocytes, which exist in the canals of Hering (terminal bile ductules). They contribute to hepatocyte regeneration and may even take over this role if the liver injury is severe and associated with an impairment of hepatocyte proliferation (for reviews, see Refs. [49],70,119,141,178). These cells can differentiate into either hepatocytes or cholangiocytes (cells that line the bile ducts). In addition to the hepatocyte proliferation associated with liver damage and regeneration, hepatic stellate cells can also change into an activated state and proliferate (for reviews, see Refs. 141,145,147). It has recently been suggested that hepatic stellate cells may constitute an additional pool of liver stem cells (for review, see Ref. 141). They express several neural and stem cell markers including GFAP (29,145) and nestin following chemical fibrosis in vivo (124). Hepatic stellate cells also express nestin in the fetal and embryonic liver (124). More recently, nestin-positive cells in fetal liver have been shown to be capable of generating spheres and differentiating into neuron-like cells in vitro (92). Intriguingly, a recent study using fate mapping strategy used mice in which GFAP promoter elements regulated Cre-recombinase with ROSA-loxP-stop-loxP-green fluorescent protein (GFP) mice to generate GFAP-Cre/GFP double-transgenic mice (192). They showed that, following liver injury, hepatic stellate cells downregulated expression

of GFAP but remained GFP-positive and became highly proliferative and transiently coexpressed markers of mesenchymal and oval cells. These transitional cells disappeared as GFP-expressing hepatocytes emerged.

Pancreas

The pancreas contains two different types of parenchymal tissue: clusters of endocrine cells called islets of Langerhans, which produce hormones, and cells forming acini connected to ducts. Acinar cells have an exocrine function and secrete digestive enzymes (FIGURE 2, E AND F). There are four main cell types in the islets, which can be classified by their secretion: α, β, δ, and PP cells secrete glucagon, insulin, somatostatin, and pancreatic polypeptide, respectively. Close to the acini, specific cells called centroacinar cells line the pancreatic ducts and secrete a bicarbonate- and salt-rich solution into the small intestine. The pancreas, like the liver, contains stellate cells (vitamin A-storing cells), although the density of stellate cells in the rat pancreas was reported to be a tenth of that in the liver (80). Pancreatic stellate cells are present in the periacinar space and have long cytoplasmic processes that encircle the base of the acinus (FIGURE 2D; for reviews, see Refs. 9, 129). They can also be found in perivascular and periductal regions of the pancreas. Similar to the liver stellate cells, mouse and human pancreatic stellate cells are quiescent under normal conditions and express GFAP (8, 12, 35).

Continued growth of islet tissue occurs after birth in rodents and humans (albeit much less than hepatocyte turnover), with additional compensatory growth in response to increased demand. β-Cells' replication via uniform self-renewal is the primary mechanism regulating β-cell mass in adult life and after pancreatectomy based on convincing lineage studies (40,60,168). Neogenesis or the budding of new islet cells from pancreatic ducts have also been reported following pancreatic injury (20,81,191), although its significance over self-replication of existing β-cells remains a matter of debate and may depend on the type of injury (for reviews, see Refs. 19,25,72,98). Regarding neogenesis, studies from two independent groups recently provided strong evidence for the existence of endogenous progenitor cells in the developing and/or injured pancreas (81,191). With the use of a regeneration model (duct ligation), Ngn3-positive progenitor cells in the ductal epithelium were activated and gave rise to islet cells including β-cells (191). Another line-age study reported that carbonic anhydrase II-expressing ductal cells acted as progenitor cells, giving rise to both islets and acini during the neonatal development period and in a regeneration model (ductal ligation) in adult mice (81). Consistent with these findings, cells in the walls of small ducts immunostained positive for the stem cell markers Oct4 and Sox2 in human pancreatic tissue (198). Nevertheless, it remains to be examined whether carbonic anhydrase II-expressing ductal cells were the cells staining for these stem cell markers. The two lineage studies mentioned above also reported that α-cells were regenerated from ductal progenitor cells. The normal turnover of α-cells has not been extensively studied compared with β-cells. Nevertheless, α-cell mass is tightly regulated during normal life as shown by changes in cell mass following diet and selective gene knockout (28, 42,185). In addition, decreased β-cell mass in diabetes is accompanied by increased α-cell mass (see Ref. 42 for references), suggesting a homeostatic mechanism to maintain islet cell mass. Nestin, one of the markers of neural progenitor cells, was found in the human and mouse pancreas and colocalized with the glucagon-positive cells (i.e., α-cells) in 4-wk-old mice (41, 78). However, based on lineage studies, nestin-positive islet cells do not appear to contribute to the population of endocrine progenitor cells in vivo (33,173).

Regarding the exocrine pancreas, acinar cells can be generated by acinar cell themselves and from ductal progenitor cells (as detailed below). Replication of preexisting acinar cells was reported to contribute to the regeneration of acinar cells but not β-cells following pancreatectomy (34). A recent study suggested that acinar cells were capable of self-renewal and that they also produced a small number of glucagon- and PECAM (an endothelial cell

marker)-expressing cells using a Bmi1-Cre-estrogen receptor (ER) lineage tracing strategy (143). These results confirm earlier studies of proliferative acinar cell populations but do not rule out another undifferentiated population contributing to this lineage, suggesting the need for additional studies. Ductal progenitor cells also regenerated acini following ductal ligation (20,81). Finally, in response to pancreatic injury or inflammation, pancreatic stellate cells are transformed ("activated") from their quiescent phenotype into myofibroblast-like cells, which actively proliferate, migrate to sites of tissue damage, contract, and possibly phagocytose (128). They are thought to contribute to pancreatic fibrosis, an accompanying pathology to pancreatic cancer as well as cancer progression (8,35,155).

Prostate

Anatomically, the mouse prostate can be divided into four lobes: ventral, dorsal, lateral, and anterior. Each prostate lobe is composed of a series of branching ducts. Each duct is divided into three segments: a proximal segment connected to the urethra, an intermediate, and a distal segment (or acinus) where the secretion is produced. Ducts are lined by a glandular epithelium embedded in a fibro-muscular stroma formed by stromal cells (FIGURE 2, G AND H). The epithelium is composed of two histologically distinct cell layers: the secretory luminal layer and the basal layer lined by a basement membrane (i.e., layer of extracellular matrix) separating the basal layer and the stroma. Three main epithelial cell types compose the epithelium: the neuroendocrine (NE), basal, and luminal. Luminal cells are columnar and secrete components of seminal fluid (for review, see Ref. 105). The basal layer is believed to be the proliferative compartment and the source of progenitor cells for luminal cell replacement (18) (for exception, see below). Between the transition from basal to luminal cells, there is a heterogeneous population of epithelial cells that migrate from the basal layer into the luminal layer identified based on the expression of mixed markers using immunohistochemistry (77, 177). This heterogeneous subpopulation of cells that express an intermediate phenotype between early progenitor basal cells and terminally differentiated luminal cells are termed intermediate cells. The NE cells are sparsely scattered between the basal and luminal layers (125). Stromal cells appear to play an essential role in epithelial cell signaling and provide several growth factors that are involved in differentiation and growth inhibition.

As mentioned above, cell replacement (in particular luminal cell replacement) occurs in the adult prostate under normal conditions or following injury. To identify the location of stem cells along the ductal system, Tsujimura et al. (174) took advantage of the slow-cycling nature of such cells (174). In this procedure, a tissue is long-term labeled with a mitotic marker such as bromodeoxyuridine (BrdU) so that all cells, including the stem cells, are labeled. This is followed by a "chase" period during which the label is diluted out from all the rapidly dividing (transit amplifying) cells but is retained by the slow-cycling cells, which can thus be identified as the "label-retaining cells" and potentially "stem cells." They identified a subpopulation of mouse prostate epithelial cells, located in both the basal and the luminal layers of proximal ductal region that were slow-cycling, exhibited a high in vitro proliferative potential, and reconstituted complex glandular structures in collagen gels. Cells located in the distal ductal epithelium were rapidly proliferating, thus representing the transit-amplifying cells. These authors proposed that epithelial stem cells are maintained in a dormant state in the proximal ductal segment and give rise to proliferating transit-amplifying cells that migrate distally to either maintain the normal prostate gland or repopulate the gland during androgen-induced regeneration by serving as an immediate source of replacement cells along the ductal axis. These findings strongly suggest that these proximal cells are the stem cells. The proximal ductal segment may thus contain a stem cell niche.

It has been hypothesized that progenitor/stem cells are located in the proliferative basal layer (18,79,83) and generate two lineage cells: transit amplifying cells-intermediate cells-luminal

cells, and NE cell precursors-NE cells (for review, see Ref. 88). In favor of this hypothesis, basal cells express a neural stem cell marker nestin, and intermediate cells express mixed markers of basal and luminal cells (77,177). However, there is recent evidence that the embryonic stem cell marker Oct4A and Sox2 are expressed by a subset of human NE cells and that these cells may be implicated in prostate cancers (see below), although NE cells normally do not proliferate (94,154). It thus remains possible that NE cells or a subtype of them are slow-cycling stem cells or NE progenitor cells. Collectively, the identity of pancreatic stem cells is still not clear, and it is not certain whether each epithelial lineage arises from distinct progenitor cells. Lineage studies in transgenic mice are required to identify the prostatic stem cells and its lineage.

Common features across systems

The brain and the peripheral organs described here display a couple of common features. First, they (except the prostate) are characterized by the presence of GFAP-expressing stellate cells, also referred to as the stellate cell system (for review, see Ref. 148). In the prostate, it would be interesting to examine whether stromal cells express GFAP. Stellate cells are quiescent under normal conditions, exhibit functions similar to those of brain GFAP-cells [i.e., astrocytes (182)], and are activated following injury. In the liver, they may be a source of stem cells similar to those in the brain neurogenic zone. Although it is too premature to draw conclusion on the "stemness" of these GFAP-stellate cells in all systems, this parallel asks for further studies. Second, we would like to propose the notion of homeostasis of cell populations. For example, in the brain, elimination of transit amplifying cells and neuroblasts resulted in increased proliferation of neural stem cells and SVZ regeneration (39). In the pancreas, a decrease in β-cell mass is accompanied with increased α-cell mass. It is possible that β-cells, like neuroblasts in the brain, can release diffusible signals that limit the self-renewal and proliferation of α-cells and neural stem cells, respectively. In the prostate, acinar (i.e., distal) epithelial cells may release a pro- or anti-mitogenic signal into the duct reaching proximal epithelium where stem cells reside.

GABAergic Signaling: Regulation of Cell and Stem Cell Proliferation

GABA, its synthesizing enzyme GAD, its degrading enzyme GABA-transaminase, $GABA_A$ receptors, GABA transporters, and vesicular GABA transporters are present not only in the CNS but also in peripheral organs (see FIGURE 1 and Table 1).

Brain

In the postnatal SVZ, a sophisticated GABAergic signaling has been revealed engaging a tight communication between GFAP-cells and neuroblasts (for reviews, see Refs. 23,24,134). Neuroblasts synthesize and release GABA (17,32,100,183). Once released, GABA activates $GABA_A$ receptors present on neuroblasts as well as GFAP cells (17,100,157,183). Released GABA is taken up by high-affinity GABA transporters in GFAP cells (17,100), as a result tightly controlling the micro-environment surrounding neuroblasts. (Although the postnatal SVZ GABAergic signaling has been best characterized in developing neural tissue, many questions remain to be addressed. For example, the GABA release mechanism from neuroblasts is unknown; the GABAergic components in transit amplifying cells have not been examined.)

GABA, acting through $GABA_A$ receptors, has been shown to limit the proliferation of GFAP cells of the adult SVZ (i.e., adult stem cells) (100) and neuroblasts (122). These studies were preformed in cultured tissue (cells and/or slices). It is thus important to examine the in vivo effect of manipulating GABAergic signaling (e.g., removal of $GABA_A$ receptor in GFAP cells) on neurogenesis.

$GABA_A$ has also been shown to limit the proliferation of neural crest cells (7), pluripotent embryonic stem cells (7), and embryonic ventricular zone radial glial cells (107). The fact that $GABA_A$ receptor's function is conserved among neural stem cells and across developmental stages (i.e., embryonic and adult) suggests that it is a robust control mechanism of proliferation.

Liver

The liver is well established to contain high concentrations of GABA that are regulated by a series of hepatic metabolic pathways (including GAD, although at lower levels than other organs) and GABA transporters (for review, see Ref. 114). The liver in particular displays high activities of GABA transaminase, the enzyme responsible for GABA catabolism (190). GABA uptake has been shown in hepatocytes, presumably via GABA transporters (rat GAT-3), but not in Kupffer cells (67,117). Hepatocytes express functional $GABA_A$ receptors, as shown by autoradiographic studies, RT-PCR, and electrophysiology (47,115). Of the different $GABA_A$ receptor subunits, β3 and ε were found to be expressed in human liver and only β3 in rat liver using RT-PCR (47). When activated, these receptors caused hyperpolarization of resting hepatocytes in a bicuculline-sensitive manner (a blocker of $GABA_A$ receptors) (115).

Functionally, exogenous GABA was shown to impair restoration of liver mass following partial hepatectomy (116). Increased $GABA_A$ receptor activity (using transfection of $GABA_A$ receptor subunits) was shown to inhibit proliferation activity of the HepG2 human hepatocellular carcinoma cell line (196). More specifically, the $GABA_A$ agonist, muscimol, dose dependently inhibited epidermal growth factor-induced DNA synthesis and enhanced the transforming growth factor β1-mediated DNA synthesis suppression in primary hepatocyte cultures (15). Collectively, these studies suggest that GABA via $GABA_A$ receptors acts as an inhibitory signal for hepatic cell proliferation. Additional studies using molecular approaches in vivo are needed to confirm this finding. In addition, there are no clear data regarding the cellular localization of GAD or other GABA synthetic enzymes in the liver. Similarly, there is no information on GABAergic components in other cell types or on the function of GABA on the proliferation of other liver cells (e.g., stellate cells or oval cells).

Pancreas

In the 1970s, a series of elegant studies reported that β-cells contain a high concentration of GABA and high GAD activity comparable to CNS level and activity (61,127,164,165). Many of these studies took advantage of the toxin streptozotocin that selectively kills β-cells to conclude that GABA was synthesized in β-cells. Later on, immunohistochemical and autoradiographic studies in rat and human pancreas confirmed that GABA and GAD were identified in islet β-cells and not in the exocrine tissue (55,63,142,158,179,180). GABA has also been proposed to be used as a marker of living β-cells (181). Nevertheless, some δ cells in human but not in rat pancreas have been shown to express GAD (132), requiring additional studies for identifying the cells synthesizing GABA in human pancreas. It is now well established that β-cells synthesize and release GABA through a vesicular pathway (170) (for review, see Ref. 51,113,153). In addition, both islet α- and β-cells express plasma membrane GABA transporters [rat GAT3 (22)], as is convincingly shown with immunohistochemistry (53).

In whole human islets, α2, β3, and γ1-subunits of $GABA_A$ receptors were detected by RT-PCR (193), which is more limited than subunits detected in the brain (α1-6, β1-3, γ1–2). $GABA_A$ receptors have been identified in guinea pig, mouse, and rat α-cells but not in rat β-cells using immunohistochemistry and patch clamp recordings (13,140,188). $GABA_A$ receptor α4-, β3-, and γ2-subunit mRNAs were detected in mouse islets using RT-PCR (13), whereas transcripts of α1–3, β1–3, and γ2 were found in rat purified α-cells but not in β-cells (21). A comparative study of $GABA_A$ receptor subunits in α-cells from different species would be necessary to

address inconsistency in these molecular data. GABA is thought to be released from β-cells acting on surrounding α-cells to regulate glucagon release via $GABA_A$ receptor activation in a paracrine manner (13,140,188) (for reviews, see Refs. 69,144). We found no data regarding GABAergic components in pancreatic stellate cells or acinar cells. There is also no information regarding the function of $GABA_A$ receptors on cell proliferation in the pancreas, although the β-cells release large amounts of GABA.

Prostate

GABA and both $GABA_A$ and $GABA_B$ receptors have been identified in the epithelial cells of the prostate (46,121). Although it is found in epithelial tissue, and specifically in neuroendocrine tissue (76), evidence that the basal cell population (which is perhaps prostate stem cells; see above) expresses functional GABA or GABA receptors is lacking. There has been substantially less literature in this region regarding GABA and signaling in the prostate, but GABA was thought normally to have a regulatory role in secretion (121). There has been no link between GABA receptor activation and proliferation in this region in normal tissue. There is, however, significant new evidence that points to GABA signaling being involved in the proliferation of cancers derived from the prostate, as detailed below.

Common features across systems

GABA and its receptors have been identified in all these organs, although their exact function in normal tissue remains unclear. The signaling components are differentially expressed on different cell types, as is the case with GABA expression in neuroblasts, and not in GFAP-astrocytes of the SVZ. GABA signaling in all these regions can also be differentially regulated during development, where proliferation is highest, although we have not explored the data here.

Although GABA may have been initially overlooked as a potential proliferation-regulating signal, there is evidence in the liver and pancreas that GABA has the potential to do so. Consistent with the idea of a homeostasis of cell population, we propose that GABA is an indicator of cell mass and acts as an anti-mitotic signal.

In the brain, the action of GABA resembles that of a feedback mechanism known to apply in stem cell niches. Upon the first stem cell asymmetric division, the microenvironment of a stem cell has changed. Molecules released by the daughter cells and subsequent granddaughter cells can feed back and influence the behavior of the stem cell, including its proliferation. This principle applies in the SVZ where the level of ambient GABA is determined by the number of GABA-containing neuroblasts and will limit excessive stem-cell proliferation and thus neuroblast production. In the liver, if hepatocytes release GABA (which needs to be verified), they may control their own proliferation via $GABA_A$ receptor activation. GABA would thus act as an autocrine negative feedback mechanism to control the overall hepatocytic mass. In the pancreas and the prostate, the function of $GABA_A$ receptors on cell proliferation remains to be examined. Nevertheless, it is intriguing to speculate that GABA release from β-cells limits the proliferation of α-cells via $GABA_A$ receptor activation.

GABA: A Regulator of Cancer Cell Proliferation

In agreement with GABA's control of cell proliferation, several reports have suggested a relationship between the GABAergic system and oncogenesis (for review, see Refs. 161, 187). GABAergic signaling is altered in cancer cells. In particular, both GABA content and GAD activity are increased in certain types of human tumors such as colon, gastric, ovarian, and breast cancers (91,111,112,120,123) (FIGURE 2 and Table 2). In addition, the π-subunit of the $GABA_A$ receptor is upregulated in sporadic breast cancer (195) and pancreatic

adenocarcinomas (86). $GABA_A$ receptors were also reported to be present, functional, and depolarizing in a rare form of cancer, human insulinoma (65). Evidence (detailed below) suggests that GABA may also control tumor cell proliferation. It has been argued that many cancers are derived from rare, self-renewal cancer stem cells, which produce rapidly dividing cells and differentiated tumors cells.

Brain tumors

Changes in GABAergic components (i.e., GABA levels and $GABA_A$ receptor expression) are not restricted to peripheral tumors but have also been reported in neurocytoma (150,159). Various glioma cell lines have been shown to express $GABA_A$ receptors, but they were thought to be predominately nonfunctional (71,176). Despite this, GABA receptor expression may be differentially regulated in vivo: one study looking at GABA binding sites in glioblastomas showed that increased malignancy was associated with decreased GABA binding (87). In contrast, Labrakakis et al. (95) showed using patch-clamp electrophysiology that human gliomas, but not necessarily glioma cells lines, have functional $GABA_A$ receptors (95). Glioma cells have also been shown in vitro and in vivo to upregulate their expression of $GABA_A$ receptors after coming in contact with neurons (160). In the same study, Synowitz et al. showed that $GABA_A$ receptor activation inhibited proliferation. A different type of brain cancer, gangliogliomas, have been shown to have downregulated $GABA_A$ receptor expression compared with control tissue; this down-regulation is often associated with the susceptibility for seizures (10). Gangliogliomas have both dysplastic neuronal and glial cell types, although they are not thought to be proliferative. Medulloblastoma cell lines also express functional GABA receptors (31).

Human hepatocellular carcinoma

There is evidence that GABA receptors play a role in the proliferation of tumor cells developing in the liver. Human hepatocellular carcinoma (HCC) show decreased levels of $GABA_A$ receptor-β3 (118). Decreased receptor expression is associated with depolarization of cancer cells compared with non-tumor-associated tissue. By inducing expression of $GABA_A$-β3 in malignant hepatic tumors in vivo, Minuk et al. (118) showed that there is an attenuation of tumor growth compared with vector-transfected controls. Evidence also shows that a different subunit $GABA_A$ receptor-α3 has an opposing role. The α3-subunit expression appears to be increased, and signaling through this receptor promotes HCC growth (101). By knocking down this subunit with shRNA, Liu and colleagues (101) demonstrated that GABA-induced proliferation of HCC cell-line HepG2 is partially inhibited. Minuk et al. (118), in their characterization of HCC in various patients, also showed upregulation of $GABA_A$-α3, whereas non-tumor tissue almost never expressed the mRNA for this subunit. The mechanisms of the opposing effects of β3 vs. α3 on HCC proliferation are yet unknown. Because of their differential expression compared with non-tumor tissue, both subunits provide viable drug targets for limited HCC growth with more limited effects on surrounding healthy tissue.

Pancreatic tumors

GABA has been shown to stimulate pancreatic cancer growth by upregulating the expression of the π-subunit of the $GABA_A$ receptor (162). In this system, GABA increased intracellular calcium levels and activated the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) cascade. As another example, human insulinomas, a more rare form of pancreatic cancer involving insulin-releasing β-cells, respond to GABA and muscimol and express functional $GABA_A$ receptors (66). Electrophysiological recordings indicate that, in this particular insulinoma, $GABA_A$ receptor activation depolarized the cells and induced release of insulin.

Prostate cancer

Patients with prostate cancer metastasis have higher prostate GABA and GAD levels compared with those without metastasis and with benign prostatic hyperplasia (BPH) (11). In addition, $GABA_A$ has been shown to regulate the proliferation of prostate cancers (1,82). Ippolito et al. (82) showed that neuroendocrine-derived cancer cells of the prostate are enriched in GABA and express functional $GABA_A$ receptors. $GABA_A$ receptor antagonist picrotoxin, in combination with other receptor antagonists, inhibited the growth of prostate cancer cells (82). Most normal, non-tumor prostate tissues express $GABA_A$ receptors in the stroma but not in the epithelial compartments, whereas 15% of prostate cancer tissue samples showed various levels of $GABA_A$ receptor expression in epithelial tissue (1). In addition, it was shown that application of $GABA_A$ receptor agonists to several human prostate cell lines increased proliferation.

Common features across systems

Consistent with the idea that GABA is a strong inhibitor of cell proliferation, disturbances in GABAergic signaling may be a sign of the cell's defensive reaction against excessive cell proliferation and tumor progression. As with HCC and its expression of $GABA_A$-α3 receptor subunit, it is thus possible that GABAergic signaling in tumor cells is altered, resulting in abnormal proliferation. However, cell- and tissue-specific expression of $GABA_A$ receptor subunits have differential effects, with some enhancing and others inhibiting proliferation. It is expected that GABA can act on two levels: regulation of *1*) tumor cells and *2*) cancer stem cell proliferation. Although this remains to be investigated in either the brain or the periphery, GABAergic signaling components such as $GABA_A$ receptors could constitute therapeutic targets to control tumor growth.

Concluding Remarks

In developing neural tissue, GABA is now well accepted as a strong negative regulator of stem-cell proliferation. In addition, it was also shown to limit the proliferation of embryonic pluripotent stem cells. GABA's action of cell proliferation is not limited to the CNS. Many components, if not all of GABAergic signaling, are present in many nonneural tissues. However, the function of GABA on cell proliferation in peripheral organs remains to be thoroughly investigated and the adult stem cells identified to draw definitive conclusions on its universal negative function on stem-cell proliferation.. Nevertheless, we speculated that GABA may control the rate of proliferation or the number of proliferative cells in each organ, allowing the maintenance of the homeostasis of the different cell populations as suggested in the SVZ.

Although GABA acting via $GABA_A$ receptors ensures a beneficial and important function on cell proliferation, a “GABAergic Mr. Hyde” has been described in different types of nonneural tumors where components of the GABAergic signaling are overexpressed. In some cases, GABA has been shown to enhance tumor cell proliferation and has even been proposed to be measured in the urine of ovarian cancer patients as a diagnostic tool (123). With more knowledge of $GABA_A$ receptor subunit expression and downstream signaling mechanisms, GABAergic signaling molecules may provide another potential target for controlling stem-cell proliferation and limiting tumor progression.

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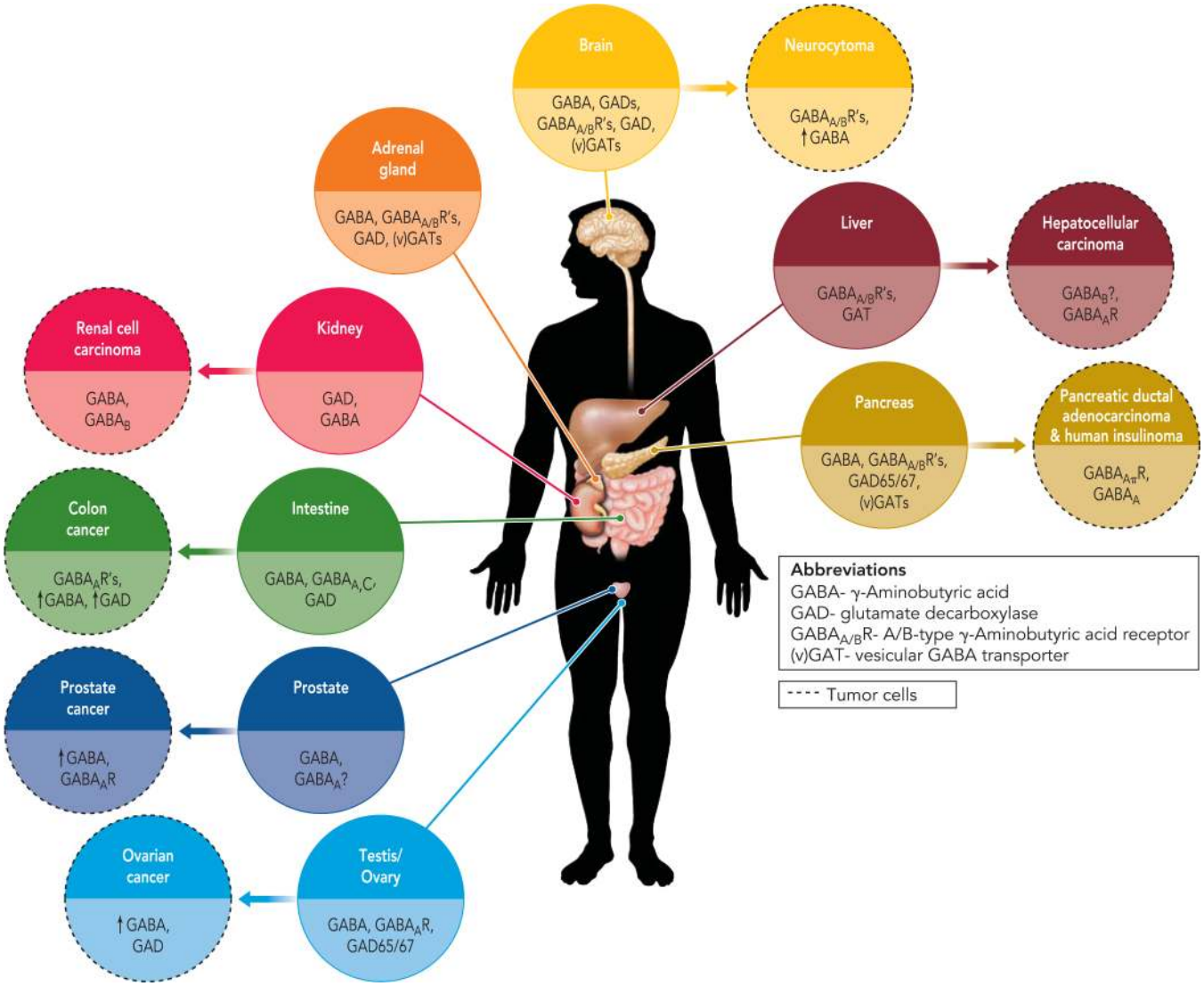

FIGURE 1. Diagram of a human body

Diagram of a human body, including filled circles highlighting the CNS and peripheral organs displaying GABAergic signaling molecules. Dotted circles highlight changes in GABAergic components in certain tumors of the CNS and peripheral organs.

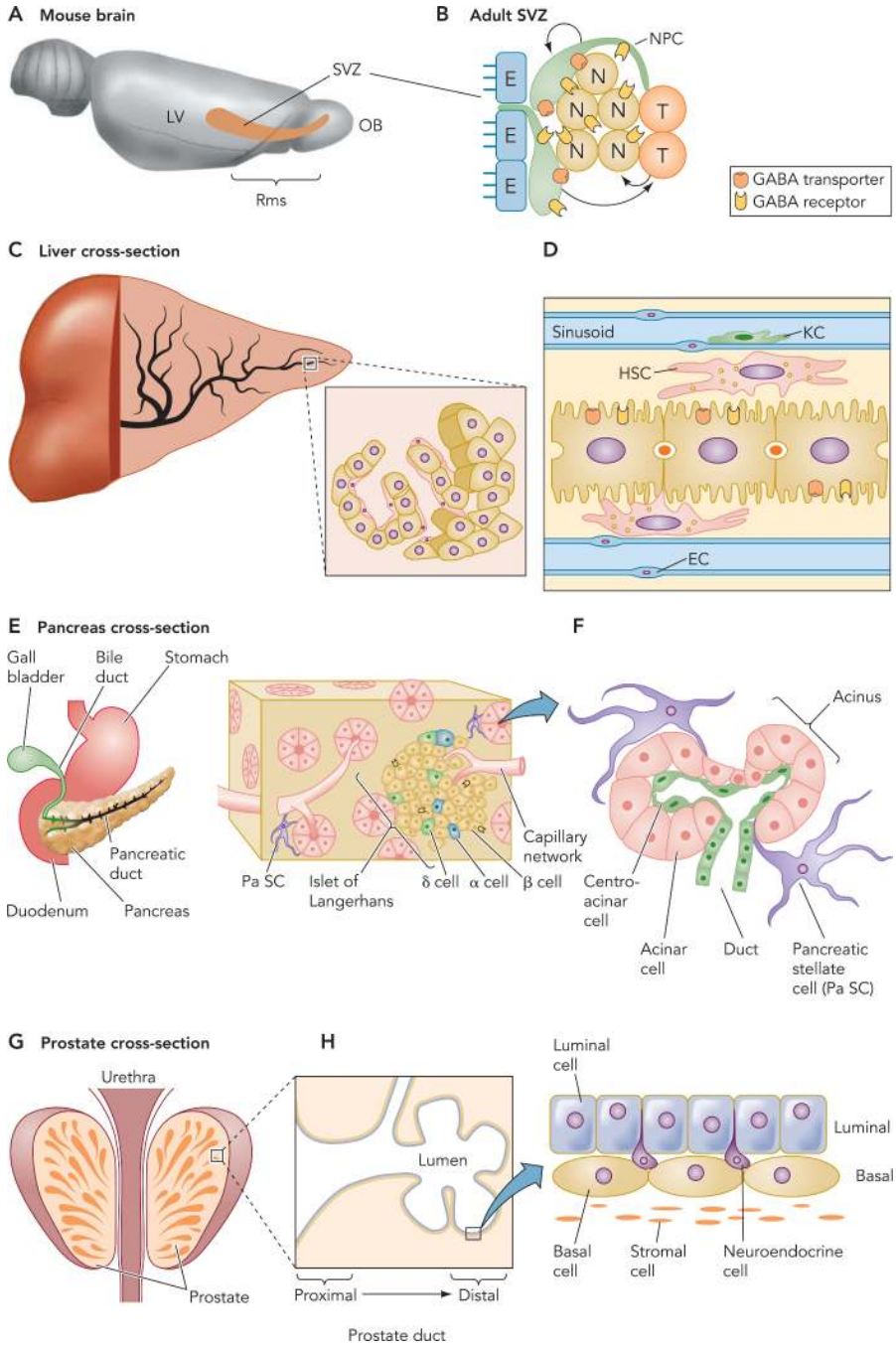

FIGURE 2. The brain and the subventricular zone

A: sagittal depiction of the brain and the subventricular zone (SVZ)-rostral migratory stream (RMS). *B*: a diagram of the adult SVZ. Ependymal (E) cells border the lateral ventricle (LV). Astrocytes (Astro) (neural stem/progenitor cells) surround a cluster of neuroblasts (N) and transit amplifying cells (T). Both astrocytes and neurob-lasts have $GABA_A$ receptors, and astrocytes also have GABA transporters. *C*: structure of a portion of a hepatic lobule. *D*: diagram illustrating the parenchymal (hepatocyte) and nonparenchymal cells in the liver. Endothelial cells (EC) form the lining of the sinusoids (S). Kuffler cells (KC) are tissue macrophages. Stellate cells lie in the space between hepatocytes and endothelial cells. Arrows and asterisks indicate a classical and new definition of the perisinusoidal space of Disse

between hepatocyte and stellate cells, respectively, and endothelial cells. $GABA_A$ receptors are expressed in hepatocytes. *E*: diagram illustrating the different cells of the pancreas in the islet of Langerhans (endrocrine pancreas) and the acini (exocrine pancreas). *F*: diagram illustrating the location of pancreatic stellate cells. *G*: cross-section of the prostate. *H*: schematic of basal and luminal cells.

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Table 1

GABAergic components and function in neural and peripheral niches

Organs	Regions	Cell Types	Stem/Progenitor Cells	GABA Signaling Components	$GABA_A$ Receptor Function	Model Systems (for GABA)
Brain	Postnatal SVZ	Astrocytes (type B)	Stem cell (gives rise to type A and C cells) (37,54,96)	R (Patch) (17,100,157,183), T (IHC) (17,100)	↓ proliferation (100,122)	Acute and culture murine slice
		Neuroblasts (type A)	Fate-committed, proliferative cell (5,103,108)	GABA/RA (Patch, Ca2 +imaging) (17,157,183)	↓ Proliferation (122) ↓ Migration (17) ↑ Maturation (56)	Cultured murine cells and slices
		Transit amplifying cells (type C)	Intermediate progenitors	ND	ND	
Liver		Hepatocytes	Fate-committed, proliferative cell (141,145) (147)	GABA/GAD (review in Ref. 114), RA (RT-PCR, AU, patch) (47,115) T (67,117)	↓ proliferation (15)	Primary rat culture, human and rat tissue, cell lines
			Putative (192) (review in Ref. 141)	ND	ND	ND
		Kupffer cells	No	None (117)	ND	ND
		Sinusoidal endothelial cells	No	ND	ND	ND
	Terminal biliary ductile[†]	Oval cells	Stem cell (generate hepatocytes, cholangiocytes) (reviewed in Refs. 49,70,119,178)	ND		
Pancreas	Islet of Langerhans	α-cells	Turnover presumably from self-renewal (28,42,185)	R_A (IHC, patch, RT-PCR) (13, 21,140,188)	[*]Inhibition of α-cell glucagon release	Isolated murine cell culture
		β-cells	Turnover from self-renewal (fate-committed, proliferative cell) (40, 60,168)	GABA/GAD (IHC, AU, GAD activity) (55,63,142,158,179, 180) T (IHC) (53)	(13,140,188) [*]Endocrine function (62)	Fixed murine slices. Rat pancreas, Cell lines
		δ-cells	ND	GAD in human (132)	ND	Rat and human pancreas, culture
		PP cells	ND	No GABA (IHC) (63)	ND	Rat tissue
	Acinus	Acinar cells	Turnover from self-renewal and possible progenitor cells of glucagon+ cells (34,143)	ND	ND	Rat fixed tissue, transgenic mice
		Stellate cells	ND	ND	ND	
	Pancreatic duct	Ductal epithelial cells	Stem cells (islet and acinar cells) (81,191) following injury	ND	ND	
Prostate		Neuroendocrine cells	ND	GABA (46), RA, RB, AR (121)	Possibly secretion (121)	Fixed rat sections
		Luminal cells	No	None	None	ND
		Basal cells	Putative stem cells (174)	ND	ND	ND
Kidney	Renal medulla	Epithelial cells	Stem cells (3)	GABA (AR, IHC, EM) (43,130, 189,194), GAD (26,189)	Modulation of contractility of urinary tract (43)	Rat and human tissue cDNA

Organs	Regions	Cell Types	Stem/Progenitor Cells	GABA Signaling Components	$GABA_A$ Receptor Function	Model Systems (for GABA)
				(review in Ref. 172), RA (western, RT-PCR, AU) (6,175), T (RT-PCR) (30,106,133)		
Testis		Interstitial (Leydig) cells	No	GAD, RA and RB (58,139) (review in Refs. 36,172)	↑ Leydig cell proliferation (36,59)	Rat and human tissue, TM3 cell line
		Spermatocytes, spermatids, sperm	Spermatocytes generate spermatids	GAD (48,171) (spermatocyte, spermatid), RA (spermatid) (58)	Sperm motility (27)	Rat, mouse tissue
		Spermatogonia	Stem cells (reviewed in Refs. 93, 126) generate spermatocytes	No GAD		

R, GABA receptor. T, GABA transporters; GAD, glutamic acid decarboxylase; IHC, immunohistochemistry; ISH, in situ hybridization; AR, autoradiographic binding; EM, electron microscopy; RT-PCR, reverse trancriptase-polymerase chain reaction; ND, not determined.

*Stellate cells are also called Ito cells, perisinusoidal cells, or lipocytes.

†Attached to the liver.

Table 2

GABA and tumors

Region	Type of Cancer	GABA Components	↑ Upregulated ↓ Downregulated	Effect on Proliferation
Brain	Neurocytoma	GABA (159), R_A (150)	↑ GABA (in 1/4)	ND
	Glioblastoma	GABA (AR) (87)	↓	ND
	Glioma	R_A (Patch) (95)	↑ In cells lines in contact with neurons (160)	Inhibition (160)
Liver	Human hepatocellular carcinoma	R_A (IHC)	↓ β3-subunit (118) ↑ α3-subunit (101)	Inhibition (β3) (118) Stimulation (α3) (101)
Pancreas	Pancreatic adenocarcinomas	R_A (RT-PCR) (86)	↑ π-subunit (162)	Stimulation (162)
	Human insulinoma (β-cell)	R_A (Patch) (66)	↑	ND
Prostate	Neuroendocrine cancer	GABA, R_A	↑ (1,82)	Stimulation (82)