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 (189). 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 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 organs (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_B, which are ligand-gated chloride channels, and its metabotropic receptor GABA_B. Our focus will be on GABA_A receptors, which...
are heterogenous (β1-3, and γ1-3) (62) and are expressed in peripheral organs (prostate (121), kidney (6, 26), bone marrow, (52, 146), and testis (114) (for review in Ref. 141). Adult stem cells (islet and acinar cells) (81, 191) following injury

### Table 1. GABAergic components and function in neural and peripheral niches

<table>
<thead>
<tr>
<th>Organs</th>
<th>Regions</th>
<th>Cell Types</th>
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<tr>
<td>Brain</td>
<td>Postnatal SVZ</td>
<td>Astrocytes (type B)</td>
<td>Stem cell (gives rise to type A and C cells) (37, 54, 94) R (Patch) (17, 100, 157, 183), T (IHC) (17, 100)</td>
<td>↓ proliferation (100, 122)</td>
<td>Acute and culture murine slice</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurone (type A)</td>
<td>Fate-committed, proliferative cell (5, 103, 108)</td>
<td>GABA/RA (Patch, Ca&lt;sup&gt;2+&lt;/sup&gt; imaging) (17, 157, 183)</td>
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<td>Cultured murine cells and slices</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>Hepatocytes</td>
<td>Fate-committed, proliferative cell (141, 143) (147)</td>
<td>GABA/GAD (review in Ref. 114), RA (RT-PCR, AU, patch) (47, 115) T (87, 117)</td>
<td>↓ proliferation (15)</td>
<td>Primary rat culture, human and rat tissue, cell lines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sinusoidal endothelial cells</td>
<td>No</td>
<td>Putative (192) (review in Ref. 141)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kupffer cells</td>
<td>No</td>
<td>None (117)</td>
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<tr>
<td>Pancreas</td>
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<td>R&lt;sub&gt;j&lt;/sub&gt; (IHC, patch, RT-PCR) (13, 21, 140, 188)</td>
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<td></td>
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<td>β-cells</td>
<td>Turnover presumably from self-renewal (40, 42, 188)</td>
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<tr>
<td></td>
<td></td>
<td>δ-cells</td>
<td>ND</td>
<td>GAD in human (132)</td>
<td>ND</td>
<td>Rat and human pancreas, culture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP cells</td>
<td>No</td>
<td>No GABA (IHC) (63)</td>
<td>ND</td>
<td>Rat tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acinar cells</td>
<td>Turnover from self-renewal and possible progenitor cells of glucagon+ cells (34, 143)</td>
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<td>ND</td>
<td>Rat fixed tissue, transgenic mice</td>
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<td></td>
<td></td>
<td>Stellate cells</td>
<td>ND</td>
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<td></td>
<td>Pancreatic duct</td>
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**Table 1 (cont.)**

**Table 1. GABAergic components and function in neural and peripheral niches**

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are heteropentamers primarily composed of α1-4, β1-3, and γ1-3 subunits (other subunits include δ, ε, θ, π, and γ) (for review, see Ref. 74). GABA<sub>β</sub> 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<sub>β</sub> receptors on stem cell proliferation. All the components of the GABAAergic 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, 106, 175, 189), intestine (137, 186), pancreas (islets of Langerhans) (21, 62, 89, 175, 193), kidney (6, 26, 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, tests, 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 GABAAergic 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 GABAAergic elements of these peripheral niches as well as references to the tests 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 GABAAergic 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

---

**Table 1 (continued)**

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</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Neuroneurocrine</td>
<td>ND</td>
<td>GABA (46), RA, RB, AR (121)</td>
<td>Possibly secretion (121)</td>
<td>Fixed rat sections</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal</td>
<td>Basal cells</td>
<td>No</td>
<td>Putative stem cells (174)</td>
<td>None</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Kidney</td>
<td>Renal medulla</td>
<td>Epithelial cells</td>
<td>Stem cells (3)</td>
<td>GABA (AR, IHC, EM) (43, 130, 189, 194), GAD (26, 189) (review in Ref. 172), RA (western, RT-PCR, ALU) (6, 175), T (RT-PCR) (30, 106, 133)</td>
<td>Modulation of contractility of urinary tract (43)</td>
<td>Rat and human tissue, TM3 cell line</td>
</tr>
<tr>
<td>Testis</td>
<td>Interstitial</td>
<td>No</td>
<td>GAD, RA and RB (58, 139) (review in Refs. 36, 172)</td>
<td></td>
<td>Leydig cell proliferation (36, 59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Leydig) cells</td>
<td></td>
<td></td>
<td></td>
<td>Rat and human tissue</td>
<td></td>
</tr>
<tr>
<td>Spermatocytes, spermatids, sperm</td>
<td>Spermatocytes generate spermatids</td>
<td>GAD (48, 171) (spermatocyte, spermatid), RA (spermatid) (58)</td>
<td></td>
<td>Sperm motility (27)</td>
<td>Rat, mouse tissue</td>
<td></td>
</tr>
<tr>
<td>Spermatogonia</td>
<td>Stem cells (reviewed in Refs. 93, 126) generate spermatocytes</td>
<td>No GAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 transcriptase-polymerase chain reaction; ND, not determined. *Stellate cells are also called Ito cells, perisinusoidal cells, or lipocytes. †Attached to the liver.

---

**FIGURE 1**

**Adult neural stem cell niches**

-- Additional text and figures related to stem cell niches and GABA signaling in the brain and peripheral organs.

**FIGURE 2**

**Adult neural stem cell niches**

-- Additional text and figures related to stem cell niches and GABA signaling in the brain and peripheral organs.
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).

The liver contains numerous live cells, i.e., the total liver occupies only 40% of the liver cells are located in the tissue (i.e., blood vessels) and a sinusoidal endothelial/macrophage, previously known to serve as live (32).

The liver is a significant organ, and injury, hepatic regeneration a critical, and proliferation is an important process. In hepatocytes, the SVZ (or bile ducts) is associated with liver injury. These SVZ cells, when exposed to hepatic injury, are activated. In particular, in the SVZ, these cells are capable of generating tumor-like cells (GFP-cells) that can form transverse astrogliosis (149, 167).

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Pancreas

The pancreas contains numerous live cells, forming a...
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, ten 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 high-proliferative and transiently compressed 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: a, b, A, 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 periportal and peribiliary 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 pancreaticectomy based on contrasting lineage studies (40, 60, 168). Neogenesis or the budding of new islet cells from pancreatic ducts have also been reported following pancreatic injury (80, 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 lineage 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 (duct ligation) in adult mice (81). Consistent with these findings, cells in the walls of small ducts immunoabsorbed 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 during 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...
Regarding the generation of endocrine progenitor cells by progenitor cells, existing autocrine regulation of pancreas regeneration was observed. Progenitor cells were also found to produce an endocrine cell-like Cre-estrogen (143). These results indicate that the undifferentiation of progenitor cells suggest that the progenitor cells act together (20, 81). For inflammation, the fibrosis, an acinar cell as well as a pancreatic cell, is known to be mediated by the activated fibroblast-like cells at sites of tissue damage (128). The fibrosis, an inflammatory reaction, is known to be mediated by the activated fibroblast-like cells at sites of tissue damage (128).

**Prostate**

Anatomically, the prostate is divided into four lobes: the prostate lobe, the seminal vesicle, the vas deferens, and the ductus deferens. Each of these lobes has an accessory gland, the seminal vesicle, and the ductus deferens. Secretions from the accessory glands are mixed with semen to form a thick, milky ejaculate. The prostate is a gland that produces a fluid which is rich in a protein called prostate specific antigen (PSA), a marker for prostate cancer. PSA is used to screen for prostate cancer, but high levels of PSA do not always mean that a person has cancer. The prostate is involved in ejaculation and, once inside the urethra, helps to force the semen out of the body. It is also responsible for maintaining the health of the reproductive tract. The prostate is a gland that produces a fluid which is rich in a protein called prostate specific antigen (PSA), a marker for prostate cancer. PSA is used to screen for prostate cancer, but high levels of PSA do not always mean that a person has cancer. The prostate is involved in ejaculation and, once inside the urethra, helps to force the semen out of the body.

**FIGURE 2.** The brain and the subventricular zone.

Regarding the exocrine pancreas, acinar cells can be generated by acinar cell themselves and from ductal progenitor cells (as detailed below). Replication of pre-existing 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 ghrelin- and PREGAN (an endothelial cell marker)-expressing cells using a Bmi1-Cre-estrogen receptor (ER) lineage tracing strategy (143). These results confirm earlier studies of prolifera- tion of NE cells in the pancreas (100), which do not rule out another undifferentiated population contributing to this lineage, suggesting the need for additional studies. Ductal pro- genitor 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 phagocyte- tise (128). They are thought to contribute to pancreatic fibrosis, an accompanying pathology to pancreatic can- cer 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 inter- mediate, 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 basalmal layer and the stroma. Three main epithelial cell types compose the epithelium: the neuroendocrine (NE), basal, and luminal. Luminal cells are columnar and secrete com-ponents of seminal fluid (for review, see Ref. 105). The basal layer is believed to be the proliferative compart- ment 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 heteroge- neous subpopulation of cells that express an interme- diate 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 iden- tify the location of stem cells along the ductal system, Tsuchimura 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, includ- ing 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 subpopula- tion 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 main- tained in a dormant state in the proximal ductal seg- ment and give rise to proliferating transit-amplifying cells that migrate distally to either maintain the nor- mal 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 pre- cursors-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 nor- mally 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
Table 2. GABA and tumors

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GABAergic Signaling: Regulation of Cell and Stem Cell Proliferation

GABA, its synthesizing enzyme GAD, its degrading enzyme GABA-transaminase, GABAₐ 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 signal has been shown to limit the proliferation of neural stem cells and SVZ regeneration (39). In the pancreas, a decrease in GABA activity has been shown to limit the proliferation of β-cells (100) and neuroblasts (122). These studies were performed 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 receptor in GABAergic cells) on neurogenesis. GABAergic pathways have 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 GABAₐ receptors’ 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 catalysis (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 GABAₐ receptors, as shown by autoradiographic studies, RT-PCR, and electrophysiology (47, 115). Of the different GABAₐ 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 (α blocker of GABAₐ receptors) (115).

In the 1970s, a role for GABAₐ receptors on β-cells was proposed (15). Collectively, these studies support the notion of homeostasis of cell populations. "stemness" of these GFAP-stellate cells in all systems, although there is no information that these GFAP cells are similar to those in the brain neurogenic zone. 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 receptor in GABAergic cells) on neurogenesis. GABAergic pathways have 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 GABAₐ receptors’ 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.

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mplifying cells and release large amounts of GABA. It is thought to be a homeostatic signal for cell proliferation, acting on stem cells in the SVZ and promoting neuroblast production in the liver. In the pancreas and the prostate, GABA and both GABAg and GABAg 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 GABAg 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 described below.

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Phylogenetic analysis of hepatic and pancreatic cells

In the brain, the action of GABA resembles that of other neuromodulators such as norepinephrine, serotonin, and acetylcholine. In the liver, the action of GABA resembles that of other neuromodulators such as norepinephrine, serotonin, and acetylcholine. However, in the pancreas, 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 GABAg-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.

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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 α-subunit of the GABA receptor is upregulated in sporadic breast cancer (195) and pancreatic adenocarcinomas (86). GABA 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 tumor cells. Therefore, the GABAergic system and oncogenesis (for review, see Refs. 161, 188) should be investigated extensively.

Brain tumors

Changes in GABAergic components (i.e., GABA levels and GABA receptor expression) are not restricted to peripheral tumors but have also been reported in neurocystoma (150, 159). Various glial cell lines have been shown to express GABA receptors, but they were thought to be predominantly nonfunctional (71, 716). 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 (187). In contrast, Larrakia et al. (95) showed using patch-clamp electrophysiology that human gliomas, glioblastomas, and medulloblastomas showed that increased malignancy was associated with decreased GABA binding (187). In contrast, Larrakia et al. (95) showed using patch-clamp electrophysiology that human gliomas, glioblastomas, and medulloblastomas have downregulated GABAA 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. Hepatocellular carcinoma (HCC) show decreased levels of GABA receptor-β3 (110). Decreased receptor expression is associated with depolarization of cancer cells compared with non-tumor-associated tissue. By inducing expression of GABAergic signaling in abnormal prostate tissue, specific expression of the differentially expressed GABA receptor may act on two levels: to control neoplastic malignancy and to control tumor growth.

Pancreatic tumors

GABA has been shown to stimulate pancreatic cancer growth by upregulating the expression of the α-subunit of the GABA 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 receptors (66). Electrophysiological recordings indicate that, in this particular insulinoma, GABA 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 patients without metastasis and with benign prostatic hyperplasia (BPH) (11). In addition, GABA 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 receptors. GABA 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 receptors, but not within the tumor stroma (2). In addition, it was shown that application of GABA receptors agonists to several normal 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 have been observed in prostate cancer. Patients with prostate cancer metastasis have higher prostate GABA and GAD levels compared with patients without metastasis and with benign prostatic hyperplasia (BPH) (11). In addition, GABA 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 receptors. GABA 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 receptors, but not within the tumor stroma (2). In addition, it was shown that application of GABA receptor agonists to several normal prostate cell lines increased proliferation.

This work was supported by the National Institutes of Health (NIH) Grants R01-DK-009974 (to D. L. Borysewicz) and R01-DK-058315 (to D. L. Borysewicz) and by the Medical Research Council of Canada (to D. L. Borysewicz). We apologize to the many researchers whose work has been cited because of space constraints.

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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, $\alpha_{1}$ 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 $I_{\text{tumor}}$ cells and $I_{\text{cancer}}$ 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 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 define 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 IVZ.

Although GABA acting via GABA-A receptors ensures a beneficial and important function on cell proliferation, a “GABAergic Mt. Hyde” has been described in different types of neoplastic 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 receptor subunit expression and downstream signaling mechanisms, GABAergic signaling molecules may provide another potential target for controlling stem-cell proliferation and limiting tumor progression.

This work was supported by grants from the National Institutes of Health (305-0425/6 and 50307481 to A. Bordey). We apologize to many whose work we could not because of space constraints.
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