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The Neural Regulation of Cancer

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Abstract

The nervous system is intimately involved in physiological processes from development and growth to tissue homeostasis and repair throughout the body. It logically follows that the nervous system has the potential to play analogous roles in the context of cancer. Progress toward understanding the crucial role of the nervous system in cancer has accelerated in recent years, but much remains to be learned. Here, we highlight rapidly evolving concepts in this burgeoning research space and consider next steps toward understanding and therapeutically targeting the neural regulation of cancer.

THE FAR REACH OF NERVES

Nerves permeate the human body, branching and tapering extensively from a central trunk to form microscopic contacts within tissues. These many nerves are integrated together with the brain and spinal cord into a functioning nervous system, which is uniquely capable of executing diverse programs from cognition to movement but also critically regulates stem cell niches throughout the body (**Figure 1**). Whether by secretion of soluble ligands like sonic hedgehog (SHH) or neurotransmitters like acetylcholine, nerves fulfill a recurring role in the formation, maintenance, and health of diverse tissues throughout development and adult life. It is now emerging that these choreographed programs of nerve-regulated organogenesis, homeostasis, and plasticity are corrupted during the earliest steps of malignant transformation and thereby potentiate cancer initiation and progression. Here, we highlight the nervous system as an integral and understudied force capable of shaping the initiation and growth of a variety of cancers such as brain, gastric, pancreatic, prostate, and skin malignancies. These recent conceptual advances regarding the neural regulation of cancer build upon decades of research firmly establishing the fundamental importance of genetic abnormalities to cancer. The etiology of nearly all cancers can be attributed, at least in part, to the influence of tumor-suppressor gene and oncogene mutations or other genetic/epigenetic aberrations (Vogelstein et al. 2013). Only recently has it become clear that this genetic basis of cancer is a necessary but insufficient conceptual framework for understanding and halting cancer growth in complex ecosystems within the body (Hanahan & Weinberg 2011, Martincorena et al. 2015). The tumor microenvironment is complex and dynamic and its impact on malignant growth is not yet fully characterized.

NEURAL REGULATION OF NORMAL STEM CELL NICHES THROUGHOUT THE BODY

Healthy, self-renewing cells of the body are physically restricted in anatomical spaces and tightly controlled by relationships with neighboring cells. While each stem cell niche is unique in terms

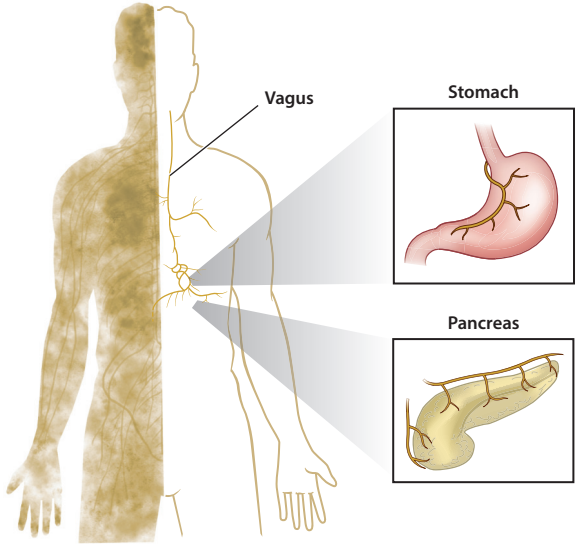

Figure 1

Peripheral nerves (*tan*) innervate visceral organs and branch extensively throughout the body. Illustration copyright SciStories LLC; adapted with permission.

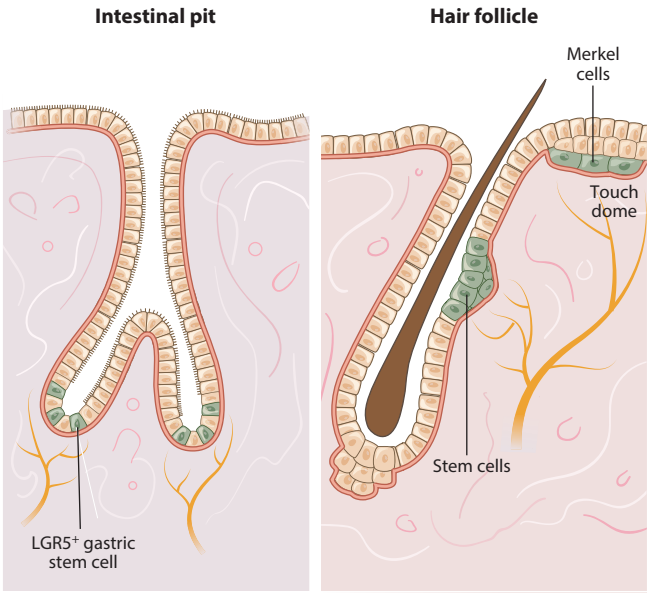

Figure 2

Peripheral nerve terminals (*yellow*) are present in and regulate stem cell niches (*green*) throughout the body. Illustration copyright SciStories LLC; adapted with permission.

of form and function, one common motif is the presence of nerve terminals (**Figure 2**). Nerves actively participate in shaping stem cell niche development, homeostasis, plasticity, and regeneration throughout the body (Boilly et al. 2017). Within these niches, populations of stem cells are arranged in particular orientations relative to neighboring cells and nerves responsible for regulating their growth. The requirement for cell-extrinsic cues to enter the cell cycle is an important check that acts to preclude uncontrolled and malignant growth. For many stem cell types, progrowth signals emanating from local nerve terminals are integral to maintenance of homeostatic stem cell population density. It now appears that this system of neural regulation is one of the first to be co-opted by incipient cancer cells on the journey to malignant transformation.

Normal tissue innervation is critical for organogenesis during development and ongoing adult tissue homeostasis. As an example, parasympathetic innervation of the nascent salivary gland is required for salivary glandulogenesis. Developmental innervation is encouraged by salivary epithelial progenitor cell secretion of neurturin, a secreted neurotrophic growth factor that recruits parasympathetic nerve growth into the nascent gland. Development of salivary acini (end buds) depends upon acetylcholine from nerves signaling through the muscarinic receptor subtype 1 (Chrm1) on epithelial progenitor cells (Knox 2010), while salivary gland tubulogenesis (formation of ducts) requires vasoactive intestinal peptide, a neuropeptide secreted by parasympathetic nerves (Nedvetsky et al. 2014). Parasympathetic denervation or disruption of acetylcholine signaling markedly reduces the number of epithelial progenitor cells and salivary acini (Knox 2010). In adulthood, cholinergic signaling continues to maintain the salivary gland epithelial precursor cell population (Emmerson et al. 2018). This role in stem cell niche maintenance explains why parasympathetic denervation limits salivary gland repair. Radiation therapy for head and neck cancers can result in damage to parasympathetic nerves and thus contributes to chronically dry mouth

(xerostomia), an important side effect adversely affecting quality of life for survivors (Emmerson et al. 2018).

Similar to the salivary gland, gastrointestinal system cholinergic signaling through muscarinic receptor subtype 3 (Chrm3) regulates the enteric stem cell niche by stimulating Wnt signaling (Hayakawa et al. 2017, Zhao et al. 2014). The importance of nerves in gastric tissue homeostasis is underscored by denervation experiments resulting in dramatic atrophy and lack of trophic responses in adult stomach (Aihara et al. 2003). Muscarinic signaling similarly regulates the intestinal (Gross et al. 2012, Lundgren et al. 2011) and hepatic (Cassiman et al. 2002) stem cell niches. This principle of innervation-dependent tissue homeostasis is recapitulated across tissue types. For example, the prostate, an organ densely innervated and regulated by parasympathetic and sympathetic nerves, undergoes prominent atrophy following surgical denervation (McVary et al. 1994) and conversely exhibits hypertrophy with adrenergic agonists (Golomb et al. 1998). The critical role of innervation extends beyond the visceral organs to the skin, where cutaneous nerves regulate hair follicle and touch dome (TD) epithelium stem cells via secretion of SHH ligand (Brownell et al. 2011, Peterson et al. 2015, Xiao et al. 2015).

PERIPHERAL NERVES PLAY DIVERSE ROLES IN PROMOTING CANCER INITIATION, SPREAD, AND ASSOCIATED PAIN

It is becoming clear that innervation critically regulates not only the normal stem cell niche but also the neoplastic niche. The first indication of this emerging principle came from observations of tumor cells invading into or growing along nerves. The phenomenon, called perineural invasion (PNI), correlates strikingly with cancer aggressiveness in a range of cancer types. Early descriptions of PNI in head and neck carcinomas noted associations with larger, less differentiated, and worse-outcome cancers (Batsakis 1985, Carter et al. 1979, O'Brien et al. 1986). Pathological examinations of prostate adenocarcinoma (Maru et al. 2001, Villers 1989) and pancreatic adenocarcinoma (Ceyhan et al. 2009, Kaneko et al. 1996, Mitsunaga et al. 2007, Takahashi et al. 1997) further defined PNI as an indicator of poor prognosis. The association between PNI and less favorable outcomes is explained, in part, by cancer cells' use of nerves as a route for metastasis (Ayala et al. 2009, Liebig et al. 2009). Beyond perineural spread, however, there is an emerging understanding that cross talk between nerves and cancer cells critically regulates tumor initiation and growth.

These early observations of PNI implicated nerves as key players in cancer pathophysiology, and recently, several seminal papers have both demonstrated the magnitude of neural influences on cancer progression and defined mechanisms mediating neural regulation of cancer. As a first indication that nerve-cancer cross talk is advantageous to cancer progression, cancer cells actively recruit nerve ingrowth to the tumor microenvironment. As neural-cancer interactions were recognized in prostate cancer early in the history of this field, we consider this tumor as a first example. In coculture models of prostate cancer and dorsal root ganglion nerves, factors secreted by cancer cells instructed axonogenesis (Ayala et al. 2001), and subsequent work has indicated that nerve growth factor (NGF) is an important secreted factor mediating this axonogenesis (Pundavela et al. 2014). NGF is the prototypical neurotrophin, a family of secreted proteins that promote growth, survival, and plasticity in the central nervous system (CNS) and peripheral nervous system (PNS); NGF plays a particularly important role in the development and maintenance of peripheral nerves. While best studied in the field of neuroscience, it is worth noting that NGF was initially discovered as a factor secreted from sarcoma cells that promotes nerve growth and survival (Cohen et al. 1954). The reciprocal growth-promoting effects of innervation on prostate cancer are evident in increased prostate cancer cell growth in the presence of nerves in vitro (Ayala et al. 2001).

Accordingly, NGF levels and nerve density in resected prostate cancer tissue correlate positively with indices of prostate cancer aggressiveness (Olar et al. 2014, Pundavela et al. 2014). These largely correlational observations have now been supported by elegant mouse models of prostate cancer that provide causal evidence of innervation-regulated prostate cancer progression. Given the dense autonomic innervation of the prostate and role of autonomic neurotransmitter signaling on normal prostate development and homeostasis, it is not surprising that autonomic neurotransmitters play critical roles in prostate cancer progression. Adrenergic (norepinephrine) signaling increases prostate cancer cell migration in vitro and in vivo (Barbieri et al. 2015), and β-adrenergic receptor blockade limits prostate cancer metastasis in prostate xenograft models (Barbieri et al. 2015, Palm et al. 2006). Elegant work by Frenette and colleagues using both xenograft and genetic mouse models of prostate cancer demonstrated that sympathetic innervation through β-adrenergic receptor signaling is required for the early stages of prostate tumor initiation (Magnon et al. 2013). Once developed, these murine models of prostate cancer exhibited prominent innervation by parasympathetic (cholinergic) nerves, and cholinergic signaling through the Chrm1 muscarinic receptor promoted prostate cancer metastasis (Magnon et al. 2013). Taken together, the available evidence underscores an important role for autonomic nervous system signaling in prostate cancer initiation and metastasis and suggests that cancer-derived axonogenic factors like NGF encourage nerve growth into the tumor to potentiate these tumor-promoting effects.

Neural regulation of enteric cancers follows a similar paradigm of bidirectional nerve-cancer cross talk. In the stomach, tumor cell secretion of neurotrophins encourages nerve ingrowth into the tumor microenvironment, and nerve-derived neurotransmitter signaling promotes cancer progression. A seminal study by Timothy Wang and colleagues demonstrated that cholinergic innervation promotes gastric cancer growth through acetylcholine-mediated stimulation of Wnt signaling, and that denervation suppresses gastric tumorigenesis (Zhao et al. 2014). Extending these exciting findings, a follow-up study by the same group demonstrated the existence of a feedforward signaling loop between cholinergic gastric nerves and enteric cancer cells (Hayakawa et al. 2017). Acetylcholine, initially supplied by enteric tuft cells and later from recruited gastric nerves, stimulates tumor NGF expression. NGF induces axonogenesis of local nerves, increased tumor innervation, and, therefore, further acetylcholine release. Acetylcholine promotes proliferation of enteric cancer cells through YAP-dependent modulation of Wnt signaling, thereby driving enteric cancer growth. Strikingly, simply driving increased NGF expression, which subsequently increases cholinergic signaling, is sufficient to initiate enteric tumors in mouse models (Hayakawa et al. 2017).

Continuing this theme, aberrantly increased innervation and neurotrophin ligand and cognate receptor expression are evident in preclinical genetic mouse models of pancreatic cancer during the premalignant stage and correlate with the early onset of abdominal pain evident in the mice (Saloman et al. 2016, Stopczynski et al. 2014). This suggests that neural influences could play a key role in pancreatic tumor initiation as well as subsequent growth, a hypothesis that has garnered support from empirical work discussed below.

The molecular mechanisms by which nerves promote cancer growth vary across different tissues, but a prominent theme is the implication of innervated stem cell niches at the origin of malignant growth. This notion is highlighted in the skin, where SHH-secreting sensory nerves contact epithelial progenitors in the TD and the bulge of the hair follicle. Although a causal role for innervation has only been demonstrated for growth of TD-derived tumors, it stands to reason that other SHH-competent stem cells within the hair follicle niche are similarly susceptible to the influence of local nerves (Brownell et al. 2011, Peterson et al. 2015, Xiao et al. 2015).

NEURAL REGULATION OF NORMAL AND NEOPLASTIC NEURAL STEM CELL NICHES: MALIGNANT GLIOMA AS AN ARCHETYPE

Neural Regulation of Neural Stem and Precursor Cells

In the CNS, electrical activity and secreted factors such as neurotransmitters and neurotrophins regulate neural stem and precursor cell function, from early brain organogenesis and throughout life. Early in brain development, before neurons have matured or synapses have formed, patterned waves of electrical activity shape neurodevelopment. At this early stage of development, depolarizing neurotransmitters are secreted, and calcium transients are found throughout the nervous system (Corlew et al. 2004, Wong 1995). In the germinal zone, gap junctions couple neural stem and precursor cells into adjacent, radially arrayed clusters during the period of cortical neurogenesis (Bittman et al. 1997, LoTurco et al. 1991). Microenvironmental signals sensed by one or more cells can affect the coupled cluster of cells. Depolarization and consequent calcium transients synchronously propagate throughout the coupled cluster (Weissman et al. 2004). Gap junctions similarly couple postnatal LV (lateral ventricle)-SVZ (subventricular zone) stem cells (Marins et al. 2009). Neurogenic precursor cell exposure to depolarizing neurotransmitters generally promotes neurogenesis, although membrane depolarization and specific neurotransmitter signaling influences the proliferation and differentiation of various neural stem/precursor cell populations in a cell-context-specific manner (Canudas 2004, Zhang et al. 2016).

In the postnatal CNS, neural stem cell niches persist throughout life in the SVZ of the LVs, third ventricle, fourth ventricle, and hippocampus. Additionally, postnatal germinal zones mediate extensive postnatal development of the cerebellum during infancy and early childhood. The SVZ of the LVs is among the best studied SVZ niche, and LV-SVZ stem cells continue to generate new olfactory bulb neurons and forebrain oligodendrocyte precursor cells (OPCs) throughout life (Hill et al. 2018, Hughes et al. 2018, Lois & Alvarez-Buylla 1994, Tripathi et al. 2017). LV-SVZ neural stem cell function is regulated by a range of neurotransmitters including glutamate, GABA (gamma-aminobutyric acid), dopamine, serotonin, and acetylcholine. Glutamate promotes LV-SVZ-derived neuroblast survival (Platel et al. 2010), while GABA, released from differentiating neuroblasts, decreases LV-SVZ neural stem cell proliferation (Liu et al. 2005). Both serotonin and dopamine promote LV-SVZ precursor cell proliferation (Banasr et al. 2004, O'Keeffe et al. 2009, Van Kampen et al. 2004). Recently, a population of neurons was discovered with processes splayed among the postnatal LV-SVZ neural stem cells and between the ependymal cell layer and the migrating neuroblasts of the LV-SVZ niche. The activity of these subependymal cholinergic neurons promotes LV-SVZ stem cell proliferation and neuroblast differentiation through local release of acetylcholine (Paez-Gonzalez et al. 2014). Similarly, in the postnatal hippocampal subgranular zone stem cell niche, neurogenesis is regulated by hippocampal neuronal activity (Deisseroth et al. 2004). In the developing cerebellum, granule cell precursor proliferation is stimulated by SHH signaling from Purkinje neurons (Wallace 1999).

Cellular Context of High-Grade Gliomas and the Relationship to Neural Stem Cell Niches

Understanding the microenvironmental regulators of normal neural stem cells is important for understanding the origins and potential regulators of malignant cancer cells. A large body of evidence now supports the idea that neural stem cells or OPCs, a unipotent stem cell type, are the cellular origin of high-grade gliomas, rather than gliomas dedifferentiating from postmitotic astrocytes, as was long assumed (Filbin et al. 2018, Lan et al. 2017, Lathia et al. 2015, Lee et al. 2018, Liu et al. 2011, Llaguno et al. 2019, Monje et al. 2011, Nagaraja et al. 2017, Suvà et al. 2014,

Tirosh et al. 2016, Venteicher et al. 2017, Zong et al. 2015). This conceptual framework is needed for the rational design of therapeutics and the intentional targeting of specific subpopulations of cancer cells within these refractory tumors.

Neural Stem Cell Niche–Glioma Interactions

Extensively interacting with neurons, stem cell niches in the postnatal brain provide a logical starting point for exploring the neural regulation of cancer in the CNS. For decades, neuro-oncologists have recognized that a preponderance of high-grade gliomas involve one or both LVs during the course of disease, a pattern that predicts a reduced time to recurrence (Chaichana et al. 2008). This pattern of glioma invasion and growth within a major neural stem cell niche is explained not only by an SVZ neural stem cell origin for some subtypes of glioma (Lan et al. 2017, Lee et al. 2018, Zong et al. 2015) but also by the demonstrated migration of glioma cells toward chemoattractant factors secreted by LV-SVZ neural stem cells (Caretti et al. 2014, Qin et al. 2017). The SVZ stem cell niche represents a reservoir for glioma recurrence, as well as a prominent site of glioma growth (Barami et al. 2009). What makes the SVZ such a rich environment for glioma growth remains to be fully elucidated, but the factors that normally regulate healthy SVZ stem cell proliferation and survival are likely co-opted by the cancer. LV-SVZ stem cells receive regulatory inputs from the cerebrospinal fluid via a primary cilium, from the blood via basal processes, and from neighboring cells via paracrine ligand–receptor interactions (Imayoshi & Kageyama 2011, Rushing & Ihrie 2016). These cells are candidate cells of origin for at least some forms of high-grade gliomas in both children and adults. A subtle yet important distinction to relate from a mouse model of adult glioblastoma is that the cell of mutation may be a neural stem cell, but the cell of transformation may be an OPC (Liu et al. 2011). In other words, mutations that arise in neural stem cells may not manifest as malignant cancer until cells progress to a more susceptible point along the trajectory of differentiation. This finding fits with clinical observations that gliomas are also present at sites distant from the LV-SVZ, suggesting direct transformation of an OPC or migration from the SVZ niche (Lee et al. 2018).

Neural Regulation of Oligodendrocyte Precursor Cells

OPCs do not reside in restricted niches but rather are evenly tiled throughout the brain parenchyma (Hughes et al. 2013). These unipotent stem cells constitute the largest self-renewing population in the adult brain and give rise to myelinating oligodendrocytes (Bergles & Richardson 2015) throughout the lifespan (Hill et al. 2018, Hughes et al. 2018, Lois & Alvarez-Buylla 1994, Tripathi et al. 2017). OPCs proliferate and generate new oligodendrocytes in response to neuronal activity (Barres & Raff 1993, Gibson et al. 2014, Hughes et al. 2018, McKenzie et al. 2014, Mitew et al. 2018). In the healthy brain, this activity-regulated OPC response enables adaptive changes in myelination, representing a mechanism by which experience modulates brain structure and therefore function (Mount & Monje 2017). Activity-regulated, adaptive myelination influences motor function (Gibson et al. 2014), motor learning (McKenzie et al. 2014), and nonmotor cognitive functions such as attention and short-term memory (Geraghty et al. 2019). While the mechanism by which neuronal activity regulates OPC proliferation and subsequent myelin changes remains to be fully defined, neuronal activity–regulated secretion of the neurotrophin BDNF (brain-derived neurotrophic factor) and subsequent signaling through the NTRK2 (TRKB) receptor on OPCs are required mechanistic components of the OPC response to neuronal activity (Geraghty et al. 2019). BDNF can also regulate OPC expression of neurotransmitter receptors (Lundgaard et al. 2013), and OPCs are also influenced by neurotransmitters (Zonouzi et al. 2015). In fact, OPCs

receive both glutamatergic and GABA-ergic synaptic input from neurons (Bergles et al. 2000, Lin & Bergles 2004). While the functional significance of these axon-glial synapses in activity-regulated myelination remains to be fully defined, they have been shown to promote OPC survival and functional maturation (Kougioumtzidou et al. 2017).

Neural Regulation of Brain Cancers

Clearly, the fate of self-renewing neural progenitors is regulated by neuronal activity. Are these microenvironmental responses mirrored by the malignant counterparts in the glioma? One recent study leveraged in vivo optogenetics to determine whether the activity of cortical projection neurons influenced the growth of patient-derived glioma xenografts. Similar to normal OPCs, pediatric and adult high-grade glioma cells responded to glutamatergic neuronal activity with increased proliferation. Mechanistic, biochemical, and proteomic analyses revealed that in addition to the secreted neurotrophin BDNF, a synaptic adhesion molecule called neuroligin-3 (NLGN3) is enzymatically cleaved at the membrane and released into the glioma microenvironment to promote glioma growth (Venkatesh et al. 2015). In a subsequent study, patient-derived high-grade glioma cells were xenografted into the brains of *Nlgn3*-knockout mice, revealing that microenvironmental NLGN3 is essential for glioma growth and progression (Venkatesh et al. 2017). While the binding partner of cleaved NLGN3 on glioma cells remains to be identified, this signaling axis represents an actionable target. In fact, the enzyme responsible for cleaving NLGN3 will be pharmacologically targeted in an upcoming clinical trial for pediatric high-grade gliomas (Pediatric Brain Tumor Consortium trial PBTC-056).

The influence of neurons on glioma growth extends well beyond the actions of NLGN3 or the mitogenic effects of BDNF, and much remains to be discovered (Gillespie & Monje 2018). There are intriguing indications in the literature that neurotransmitters like serotonin, dopamine, and glutamate may play critical roles in driving malignancy (Dolma et al. 2016; Ishiuchi et al. 2002, 2007; Lyons et al. 2007; Mahe et al. 2004; Takano et al. 2001). In contrast, the major inhibitory neurotransmitter in the CNS, GABA, appears to suppress adult glioblastoma growth (Blanchart et al. 2017), consistent with the observation that GABA receptor expression decreases with increasing glioma grade in adult glial malignancies (Labrakakis et al. 1998). Further suggesting a growth-inhibitory role, GABA-ergic interneurons are decreased in number in the glioma microenvironment (Campbell et al. 2015).

The actions of neurotransmitters on glioma cell behavior has until recently been conceptualized as autocrine or paracrine signaling. However, recent studies have also demonstrated bona fide glutamatergic, AMPA receptor (AMPA-R)-mediated neuron-to-glioma synapses in both pediatric and adult high-grade gliomas (Venkataramani et al. 2019, Venkatesh et al. 2019). Leveraging electron microscopy, whole-cell patch clamp electrophysiology, and calcium imaging techniques, two groups independently discovered the synaptic and electrical integration of glioma cells into neural circuits. As glioma cells become coupled via gap junction–mediated interconnections (Osswald et al. 2015, Venkataramani et al. 2019, Venkatesh et al. 2019), this synaptic circuit integration creates functional networks between neurons and malignant glioma cells. In a potential point of convergence between the neural regulation of cancer and the cancer stem cell state, synaptically connected pediatric glioma cells may be restricted to the OPC-like compartment of the tumor (Venkatesh et al. 2019). Glioma cell membrane depolarization, achieved experimentally using optogenetic techniques, robustly promotes glioma proliferation (Venkatesh et al. 2019), indicating a voltage-sensitive mechanism of glioma growth that echoes the depolarization-dependent regulation of neural precursor cell development discussed above. Blockade of glutamatergic signaling through dominant-negative AMPA-R expression or pharmacological inhibition using

an AMPA-R-blocking antiepileptic drug impeded high-grade glioma xenograft growth, indicating the functional role of electrochemical communication in glioma progression and highlighting a new avenue for glioma therapy (Venkatesh et al. 2019). Notably, the unexpected dependency of glioma progression on NLGN3 in the glioma microenvironment (Venkatesh et al. 2017) may be explained in part by a role in promoting the formation of neuron-to-glioma synapses. NLGN3 triggers the expression of synapse-related genes in glioma cells (Venkatesh et al. 2017) and promotes neuron-to-glioma synaptogenesis (Venkatesh et al. 2019). High-grade gliomas are the most common cause of primary brain tumor–related death in adults but are much less common than lethal brain metastases that originate from cancers outside the CNS (Achrol et al. 2019). This pattern begs the question of whether brain metastases similarly integrate into and co-opt neural circuitry to fuel their growth. In fact, breast and lung carcinoma brain metastases couple themselves to normal astrocytes via gap junctions to derive critical trophic support from the neural microenvironment (Chen et al. 2016). Even more surprising, a recent report has detailed the ability of breast-to-brain metastases to mimic astrocytic behavior at the synapse, with cancer cell processes replacing astrocytic counterparts to form pseudo-tripartite synapses (Zeng et al. 2019). In this perisynaptic position, the breast cancer cell receives glutamatergic signals that promote growth of the metastasis (Zeng et al. 2019). While it is sobering to confront the reality that both primary brain tumors and brain metastases benefit from the neural microenvironment, these conceptual advances will enable researchers to develop novel therapies for malignancies that have thus far proven largely incurable.

Glioma Influence on Neuronal Activity

Just as neuronal activity promotes glioma growth, gliomas increase neuronal activity. Increased neuronal excitability has been demonstrated in preclinical models of both adult glioblastoma (Buckingham et al. 2011, Campbell et al. 2012, Lin et al. 2017) and pediatric high-grade glioma (Venkatesh et al. 2019). Intraoperative electrocorticography recordings from awake, resting human subjects with cortical glioblastoma just prior to tumor resection confirm neuronal hyperexcitability in the glioma-infiltrated human brain compared to the more normal appearing adjacent cortex (Venkatesh et al. 2019). As the primary excitatory neurotransmitter in the brain, glutamate stands out for its known role in promoting neuronal excitability. In fact, this function of glutamate is implicated in these bidirectional interactions between neurons and glioma cells. Several studies have reported increased levels of extracellular glutamate in and around adult gliomas in vivo. This elevation in extracellular glutamate, which is due to glioma cell secretion of glutamate via a glutamate-cysteine transporter, provides one plausible explanation for the common clinical feature of seizures in subjects with glioma (Buckingham et al. 2011, Campbell et al. 2012, Ullrich et al. 2015, Ye & Sontheimer 1999). Further promoting neuronal excitability, a decrease in inhibitory interneurons, together with altered response to GABA in excitatory neurons, has been described in the microenvironment of patient-derived adult glioblastoma xenografts (Campbell et al. 2015). Even more surprising, an entirely different mechanism for promoting neuronal excitability and epileptiform discharges in the tumor-affected brain appears at play in a recently reported mouse model of adult glioblastoma (Lin et al. 2017). In this model, a subpopulation of synaptogenic glioma cells emerges as the tumor progresses. Like normal astrocytes, this subpopulation of glioma cells is characterized by expression of secreted factors that promote synaptogenesis. The emergence and expansion of this synaptogenic subpopulation coincided with the onset and increasing severity of seizure activity in the mice. Increased neuronal excitability induced by glioma cells results in further activity-regulated release of glioma growth factors such as BDNF and NLGN3 and stimulates electrochemical signaling to the tumor cells, creating a feedforward

cycle promoting glioma growth. Thus, normal neurons in the microenvironment and glioma cells are engaged in a reciprocal feedback loop as the tumor grows. From this, it is tempting to extrapolate that promotion of seizure activity is advantageous to tumor growth. Therefore, better understanding of the interplay between normal neurons and glioma cells in a native microenvironment is likely a prerequisite for uncovering targetable susceptibilities. The studies described thus far focus on glioma progression, but whether neurons regulate glioma initiation remains an open and intriguing question. Leveraging new neuromodulatory tools in systems neuroscience may be required to test the role of neuronal activity in glioma initiation, as the brain cannot be surgically denervated. Unlike the CNS, the PNS is amenable to straightforward perturbations such as surgical transection of a nerve to sever the neural influence over a particular organ, such as the salivary gland or the stomach.

TOWARD A SYSTEMS-LEVEL VIEW OF THE NEURAL REGULATION OF CANCER

Reciprocal Signaling Between Cancer Cells and the Neural Microenvironment

Our understanding of the neural regulation of cancer is still maturing, but some essential concepts may be distilled from the accumulation of several groups' observations across organ systems and tumor types. The influence of the nervous system on cancer cells is reciprocated by cancer-derived factors that invite or augment nerve growth, function, and invasion (**Figure 3**).

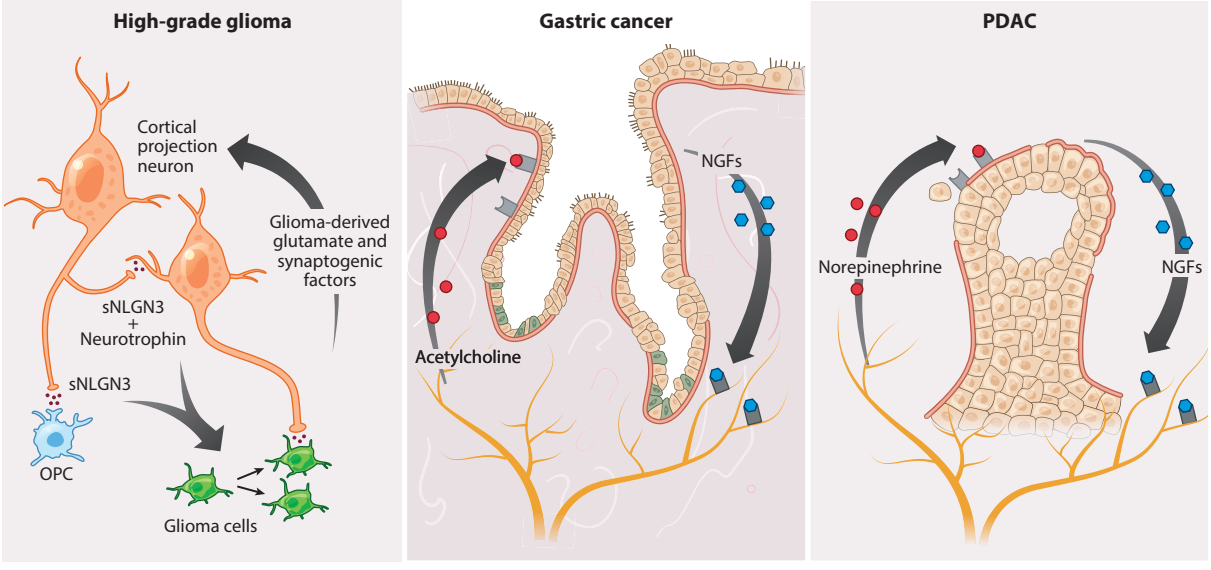

Figure 3

Cancer cells in multiple tumor types engage in cross talk with the neural microenvironment. In the central nervous system, malignant glioma cells secrete factors that promote neuronal excitability, while in tissues outside of the central nervous system, cancer cells secrete factors such as NGF (*blue hexagons*) that promote axon ingrowth into the tumor microenvironment. Neurons (nerves) release molecules that promote cancer progression, including neurotrophins, sNLGN3 (in the case of malignant glioma), and neurotransmitters (*red circles*) such as glutamate, acetylcholine, and norepinephrine in the cases of glioma, gastric cancer, and pancreatic cancer, respectively. In central nervous system cancers such as high-grade gliomas, functional glutamatergic synapses form between neurons and malignant cells. Abbreviations: NGF, nerve growth factor; OPC, oligodendrocyte precursor cell; PDAC, pancreatic ductal adenocarcinoma; sNLGN3, soluble form of neuroligin-3. Illustration copyright SciStories LLC; adapted with permission.

As discussed above, this is exemplified in the CNS by glioma cells that secrete factors to promote network excitability (Buckingham et al. 2011, Lin et al. 2017), which in turn promotes malignant growth (Lawn et al. 2015; Venkatesh et al. 2015, 2017, 2019). In the PNS, both the parasympathetic (cholinergic) and sympathetic (adrenergic) arms of the autonomic nervous system engage in analogous feedforward relationships with malignant cells in the stomach and pancreas, respectively. In the stomach, local cholinergic nerve terminals and $ChAT^{+}$ tuft cells provide incipient gastric cancer cells with acetylcholine, which signals through muscarinic receptors to promote tumor growth and further nerve infiltration via cancer cell NGF secretion (Hayakawa et al. 2017). In the pancreas, innervating adrenergic nerves release norepinephrine, which binds to β-adrenergic receptors on transforming acinar cells to augment their secretion of NGF and growth via PERK signaling (Renz et al. 2018). Clearly, the molecular mechanisms by which nervous system activity modulates tumor growth vary across organ systems. Despite these differences in signaling molecules, cell types, and neurotransmitters, a common pattern is evident. The bidirectional signaling relationships detailed above are no doubt integral to the neural regulation of cancer and unfold in the local microenvironment.

Systemic Stress is Translated into Cancer Growth

The critical relevance of autonomic innervation to tumor inception and growth is perhaps surprising at first glance. In a simplistic sense, the sympathetic and parasympathetic arms of the autonomic nervous system independently and antagonistically regulate the "fight or flight" and "rest and digest" programs, respectively. Under normal conditions, these systems keep one another in check, but this balance is disrupted when any number of real or perceived stresses are encountered, including injury or illness. Stress, and the associated systemic physiological response, is translated into biochemical signals at the level of individual cells and has direct consequences for cancer cell behavior. In fact, there is strong evidence for systemic influences of the nervous system even in nonmetastatic cancers. Several studies have now convincingly demonstrated the potent effect of stress and the subsequent elevation in circulating stress-related hormones/neurotransmitters on the development and progression of cancer. To recapitulate a physiological response in a controlled experimental setting, researchers widely use chronic restraint stress (CRS) as a means to elicit responses from both the sympatho-adrenomedullary and hypothalamic-pituitary-adrenocortical (HPA) pathways (Ulrich-Lai & Herman 2009). In the former pathway, commonly known as "fight or flight," sympathetic nerves and the adrenal medulla rapidly (in seconds) induce organism-wide changes via catecholamine (epinephrine and norepinephrine) secretion in response to actual or perceived stress. In contrast, the HPA pathway functions via slower hormonal (glucocorticoid and mineralocorticoid) mechanisms and in the short-term largely reinforces faster catecholamine responses. Using CRS, several groups have established that systemic stress promotes oncogenesis in the breast, ovaries, pancreas, and prostate via activity of the sympathetic nervous system (SNS) (Cui et al. 2019, Hassan et al. 2013, Kim-Fuchs et al. 2014, Partecke et al. 2016, Renz et al. 2018, Thaker et al. 2006). Mechanistic details from each study highlight points of convergence along signaling pathways and potentially vulnerable nodes, but also make abundantly clear that much remains to be learned about the neural regulation of cancer. For instance, cAMP-PKA signaling is recurrently implicated downstream of β-adrenergic receptor signaling, but this cascade appears capable of directing programs as diverse as angiogenesis through the activity of VEGF or resistance to apoptosis via BAD phosphorylation (Sastry et al. 2007, Thaker et al. 2006, Zahalka et al. 2017). An entirely distinct signaling circuitry is thought to be downstream of stress-induced β-adrenergic receptor signaling in a mouse model of breast cancer. In that case, adrenergic signaling induced a metabolic shift toward lactate production and

stabilization of a Myc-driven stem-like transcriptional program in tumor cells (Cui et al. 2019). Altogether, these observations highlight a growing appreciation for the involvement of stress in cancer as it is mediated by the SNS. A more nuanced question relates to the relative contributions of norepinephrine secreted from local sympathetic nerve terminals within tumor microenvironments and the circulating catecholamines released from the adrenal medulla as a result of chronic stress. To address this point, one recent study determined that surgical removal of the adrenal glands reversed the stress-induced potentiation of a Kras-driven mouse model of pancreatic ductal adenocarcinoma (Renz et al. 2018). Another group performed splanchic denervation to demonstrate that circulating epinephrine was dispensable for stress-induced metastatic spread in a mouse model of breast cancer (Walker et al. 2019). One logical conclusion from these reports is that the dramatic impact of SNS activity on tumor growth and progression appears to vary with distinct tumor types and microenvironments.

Like the reciprocal signaling demonstrated in the local tumor microenvironment (as in **Figure 3**), mutual interactions occur at the systems level as well. Both the sympatho-adrenomedullary and HPA signaling axes are known to exert numerous and far-reaching influences over various cancer types. While the complex interplay between these regulatory systems and the tumor microenvironment is beyond the scope of the present discussion, these many concepts were recently synthesized in a comprehensive and well-written review (Cole et al. 2015). From these concepts, it is clear that the hypothalamus is intimately involved with system-level changes during the development of cancer. A newer concept is that cancers themselves may perturb hypothalamic function. Beyond the illness and stress-induced stimulation of HPA function, recent work has found complex systemic influences of cancer on hypothalamic regulation of sleep and hepatic glucose metabolism (Borniger et al. 2018). Borniger et al. discovered in a mouse model of breast cancer that tumor cells induced dysregulation of satiety hormones, in turn altering activity of hypocretin/orexin neurons that, signaling in part through the SNS, ultimately caused disruptions to normal circadian rhythms and energy utilization. The results from this pioneering study provide tantalizing hints as to the potential breadth of nervous system involvement in cancer progression. Given these exciting findings, current and future research efforts should be focused on dissecting the relative contributions of local and systemic nervous system influences in shaping and directing the initiation and progression of cancers (**Figure 4**). Such studies will require the adoption of concepts, tools, and techniques from neuroscience; efforts to foster collaborations between cancer biologists and neuroscientists is paramount to making progress in this exciting intersectional space.

Nerves regulate stem cell niche dynamics, form the basis of cognition, and choreograph system-wide fight-or-flight responses. The nervous system accomplishes these feats in coordination with other body systems such as the vascular, endocrine, and immune systems (Chavan et al. 2017). This exquisitely intricate choreography underlying normal physiology is disrupted during oncogenesis in ways that are not yet fully understood. In some cases, an aberration may be inferred from mutational landscapes, such as the functionally crucial constitutive activation of neurotrophin receptor kinases in Trk fusion–driven malignancies (Cocco et al. 2018). Genetic aberrations are centrally involved in the malignant transformation of normal cells, but the nervous system is revealing itself to influence events via nongenetic means at each step along the way. Denervation studies in a growing number of solid cancer models have conclusively demonstrated the capacity of the nervous system to potentiate oncogenesis via autonomic signaling in those cancers (Magnon et al. 2013, Renz et al. 2018, Zhao et al. 2014). Pharmacological and genetic blockade of β-adrenergic or cholinergic signaling is sufficient to stymie the growth of several mouse models of cancer. Still, such progress in clarifying a causal role for nerves in cancer initiation or progression highlights the nascent conceptual link between the cancer stem cell model and the neural regulation of

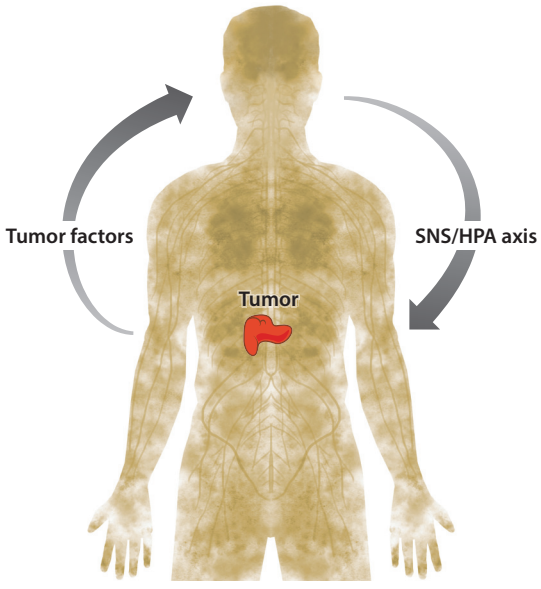

Figure 4

Emerging evidence for systemic feedback between tumors and the nervous system (*tan*). Abbreviations: HPA, hypothalamic-pituitary-adrenocortical; SNS, sympathetic nervous system. Illustration copyright SciStories LLC; adapted with permission.

cancer. The cancer stem cell model has proven to be a robust conceptual framework for describing the diversity of cellular states and behaviors inherent to many human tumors, but how various microenvironmental factors influence the induction or persistence of these states is very much an area of active study. Only recently have researchers begun deciphering the complex interplay between genetic, epigenetic, metabolic, and microenvironmental factors that influences the behavior and fate of cancer cells (Mack et al. 2015). Similar to healthy stem cell niches, it appears that the cancer stem cell state is not simply genetically encoded, but rather arises from a summation of cell-intrinsic programs and microenvironmental cues (Batlle & Clevers 2017, Kreso & Dick 2014). Accumulating evidence suggests that the nervous system is one critical mediator of the cancer stem cell state across numerous malignancies (Hayakawa et al. 2017, Peterson et al. 2015).

While illustrative, examples such as Trk fusion–positive malignancies belie the complexity and nuance of selective pressures in a dynamic tumor ecosystem. Natural selection acts on phenotype rather than genotype, and there is increasing clarity that a cancer cell's phenotype is only partially dictated by genetics. Here again, malignant glioma provides an archetype to describe the layers that together comprise a given cancer cell's identity and fitness. It has been accepted for some time that specific mutational subclasses of high-grade gliomas are characterized by gene expression programs that resemble various stages along a normal neurodevelopmental trajectory (Phillips et al. 2006, Verhaak et al. 2010). The advent and application of single-cell sequencing technologies have enabled the deconvolution of these molecular signatures at unprecedented resolution. It is now clear that high-grade gliomas in children and adults are mosaics of genetic subclones, each one supporting a diverse repertoire of transcriptional states that strongly resemble normal neurodevelopmental hierarchies (Filbin et al. 2018, Patel et al. 2014, Venteicher et al. 2017). Amplification of epidermal growth factor receptor (EGFR) and inactivation of neurofibromin 1 (NF1) are genetic

hallmarks of adult glioblastomas, which are the most aggressive malignant gliomas of adulthood. These aberrations strongly influence, but do not solely dictate, the transcriptional identity of a cancer cell in vivo. For instance, EGFR amplification promotes the adoption of an astrocyte-like phenotype in glioma cells, while inactivation of NF1 facilitates induction of a mesenchymal-like phenotype (Neftel et al. 2019). Importantly, cancer cells of a given genotype exhibit the plasticity to transition from one transcriptional state to another within a dynamic microenvironment (Neftel et al. 2019). Presumably, these states are transiently acquired and relinquished via genetic aberrations encoded in the cancer cells in concert with variable signals emanating from the microenvironment. Collectively, the emerging data support a model in which genetically defined glioma cells are predisposed to assume a given transcriptional and phenotypic identity but retain the capacity to assume alternate functional states within a shifting landscape of selective pressures as tumors progress in the microenvironments that support their growth. Determining whether and how these different transcriptional identities influence cancer inception and growth has clear implications for the design and implementation of new therapies for these currently incurable malignancies.

The evidence outlined here suggests an outsize role for nervous system–derived microenvironmental cues in directing behavior of normal and neoplastic stem cells. Our understanding of the neural regulation of cancer as a potent force in the development and growth of cancers is maturing. The extent to which the nervous system directly influences cancer stem cell dynamics or indirectly impacts cancer growth via modulation of the immune response is an issue worthy of intense inquiry. The summation of these observations across organ systems and cancer types suggests that the neural regulation of cancer must be integrated into a holistic view encompassing the entire body, each part of which is sensed and regulated by the nervous system.

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