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Neural Signaling in Cancer

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Abstract

Nervous system activity regulates development, homeostasis, and plasticity of the brain as well as other organs in the body. These mechanisms are subverted in cancer to propel malignant growth. In turn, cancers modulate neural structure and function to augment growth-promoting neural signaling in the tumor microenvironment. Approaching cancer biology from a neuroscience perspective will elucidate new therapeutic strategies for presently lethal forms of cancer. In this review, we highlight the neural signaling mechanisms recapitulated in primary brain tumors, brain metastases, and solid tumors throughout the body that regulate cancer progression.

Contents

INTRODUCTION

Nervous system activity regulates development, homeostasis, and plasticity in tissue types throughout the body (Harris 1981, Venkatesh & Monje 2017). This is best studied in the brain, but similar principles of neuronal activity regulating tissue stem cell niches extend to a wide variety of organs (Boilly et al. 2017, Venkatesh & Monje 2017). Given this emerging understanding of the roles of innervation in development and regeneration, it is perhaps not surprising that the nervous system plays critical roles in the regulation of cancer. Cancer—the uncontrolled growth and spread of abnormal, dysregulated cells by acquisition of one or more oncogenic mutations that typically arise from tissue stem or precursor cells—tends to recapitulate and hijack mechanisms of development and growth normally employed by the cell type from which it originates. As discussed in this review, the activity of central and peripheral nervous system neurons regulates both normal and malignant tissue development and growth. The emerging field of cancer neuroscience has elucidated central roles for the nervous system in the pathophysiology of primary brain tumors, brain metastases, and solid tumors in organs throughout the body. Here, we highlight recent evidence demonstrating a dynamic, bidirectional interaction between the nervous system and cancer.

ELECTRICAL ACTIVITY IN NEURODEVELOPMENT

To understand how neuronal activity alters the behavior of cancer cells in the central nervous system, it is helpful to revisit the role of activity in the context of neural development and plasticity. Development of the complex, functionally diverse and precisely tuned nervous system broadly involves the steps of neural induction, regionalization, neurogenesis (the generation of neurons) and gliogenesis (the generation of astrocytes and oligodendrocytes) from neural stem and precursor cells, cellular migration and differentiation, synaptogenesis and synaptic pruning, and myelination. Changes in cellular membrane potential and depolarization-induced calcium waves play a central role in each step of nervous system development, even before mature neurons have formed or circuits have assembled. In the earliest phases of neural induction, propagating waves of calcium transients have been observed in the dorsal marginal zone and neural ectoderm (Webb et al.

2005), which causes a switch in these tissues from an epidermal to neural fate (Leclerc et al. 1997, 2001). Waves of depolarization and consequent calcium transients are critical for both cellular and synaptic patterning. In the developing prenatal cerebrum, neural stem cells in the germinal zone are coupled by gap junctions that enable membrane depolarization–induced calcium transients to propagate synchronously. Such waves of depolarization regulate neural stem cell proliferation during corticogenesis (Bahrey & Moody 2003, Bittman & LoTurco 1999, Bittman et al. 1997, Weissman et al. 2004). Neurotransmitter-induced membrane depolarization results in calcium influx at voltage-gated calcium channels that can affect a range of cellular functions (Bito et al. 1996; Deisseroth et al. 1996, 1998). Secretion of the neurotransmitters glutamate and γ-aminobutyric acid (GABA) in a nonsynaptic manner during early development exposes neurogenic stem and progenitor cells to depolarizing signals; GABA acts as an excitatory neurotransmitter in the developing brain due to a predominance of NKCC1 relative to KCC2 cotransporter expression and consequently elevated intracellular chloride concentrations (Ben-Ari et al. 1989, Rivera et al. 1999).

Depolarizing neurotransmitters generally promote neurogenesis, although the precise response of a given neural stem/precursor cell population is context specific, and neurotransmitter-induced depolarization may alternatively promote cell proliferation or differentiation depending on the location and identity of the neural stem/precursor cell population (Canudas et al. 2004, LoTurco et al. 1995, Luk & Sadikot 2004, Platel et al. 2010). Like new neuron production, voltage-dependent mechanisms regulate neuronal subtype specification. For example, cortical neuronal subtype specification is regulated by the resting membrane potential of ventricular zone progenitors (Vitali et al. 2018). Neuroblast migration is also influenced by voltage-dependent mechanisms, including developmental migration of interneurons (Bortone & Polleux 2009, De Marco García et al. 2011). Transient glutamatergic synapses from subplate neurons onto migrating immature neurons regulate radial migration during corticogenesis (Ohtaka-Maruyama et al. 2018). Similarly, electrical activity regulates the morphological maturation of neurons, including dendritic arborization (Cancedda et al. 2007), axonogenesis, and axon pathfinding (Wang et al. 2007), and augments growth cone responses to attractant and repellent cues (Ming et al. 2001) to target long-range axons to specialized cortical regions and their appropriate laminar layers therein (Catalano & Shatz 1998, Dantzker & Callaway 1998).

Just as gap junctions couple neural stem/precursor cells in the prenatal brain, in the early postnatal nervous system, migrating neuroblasts also exhibit gap junctional coupling (Marins et al. 2009), as do neurons in the retina (Penn et al. 1994), prenatal and early postnatal neocortex (Bahrey & Moody 2003, Peinado et al. 1993), and auditory system (Tritsch et al. 2007). Such gap junctional coupling, extrasynaptic glutamate secretion, and pacemaker neurons (for review, see Blankenship & Feller 2010) are mechanisms that enable synchronized, action potential–dependent calcium transients to spread through the nascent neocortex (Corlew et al. 2004), retina (Meister et al. 1991, Wong et al. 1995), hippocampus (Garaschuk et al. 1998, Leinekugel et al. 2002), cerebellum (Watt et al. 2009), and auditory system (Lippe 1994, Tritsch et al. 2007). These experience-independent, coordinated waves of activity promote neural circuit assembly through the Hebbian principle (Hebb 1949). Experience then refines the connectivity of functional circuits (for review, see Katz & Shatz 1996, Kirkby et al. 2013).

The important roles that voltage-dependent mechanisms play in neurodevelopment are underscored by neurodevelopmental malformations caused by mutations in genes encoding ion channels. Cortical malformations called polymicrogyria can be caused by *N*-methyl-D-aspartate (NMDA) receptor subunit mutations (Fry et al. 2018, Platzer et al. 2017) or by mutations in *SCN3A*, a gene coding for voltage-gated sodium channel Nav1.3 (Smith et al. 2018). Similarly,

neuroblast proliferation is regulated by voltage-gated sodium channels in *Drosophila* (Piggott et al. 2019).

The influence of neuronal activity on neural stem and precursor cells continues throughout life. Glutamatergic and GABAergic neuronal activity promotes neurogenesis in the dentate gyrus of the adult hippocampus (Deisseroth et al. 2004, Tozuka et al. 2005). In the subventricular zone of the lateral ventricles, which persists as a germinal region, a range of neurotransmitters can influence postnatal neurogenesis, including GABA (Liu et al. 2005), dopamine (O'Keeffe et al. 2009), serotonin (Banasr et al. 2004), and acetylcholine. Acetylcholine is released from subependymal projections of cholinergic neurons in an activity-dependent manner, which promotes subventricular zone neural stem cell proliferation and the differentiation of neuroblasts (Paez-Gonzalez et al. 2014).

Activity also influences gliogenesis and plasticity of myelin, the insulating ensheathment produced by oligodendrocytes that allows rapid saltatory conduction of action potentials (Huxley & Stämpeli 1949) and also provides metabolic support to underlying axons (Fünfschilling et al. 2012). Oligodendrocytes are derived from glial progenitors called oligodendrocyte precursor cells (OPCs) that constitute approximately 5–10% of all cells in the nervous system and are evenly distributed across the brain and spinal cord in a tiled pattern that maintains spatial domains (Hughes et al. 2013). Following the protracted process of developmental myelination—spanning at least three decades in humans (Flechsig 1920, Lebel et al. 2012, Yakovlev & Lecours 1967)—generation of new oligodendrocytes continues throughout the life span (Hill et al. 2018, Hughes et al. 2013, Peters & Sethares 2002, Tripathi et al. 2017, Young et al. 2013), and myelin continues to accumulate in certain brain regions such as the neocortex and intercortical projections (Flechsig 1920, Yakovlev & Lecours 1967). Early studies in rodent optic nerve found that neuronal activity is linked to OPC proliferation, as proliferation was decreased just a short time after either optic nerve transection or silencing with intravitreal injection of tetrodotoxin (Barres & Raff 1993). Recent work has demonstrated that neuronal activity modulates myelin development (Hines et al. 2015, Mensch et al. 2015) and promotes adaptive myelin changes throughout life (Gibson et al. 2014, Hughes et al. 2018, Mitew et al. 2018) that tune neural circuit function (Noori et al. 2020, Pajevic et al. 2014, Steadman et al. 2020) and contribute to neurological functions, including learning and memory (Geraghty et al. 2019, Gibson et al. 2014, McKenzie et al. 2014, Pan et al. 2020, Steadman et al. 2020). Communication between neurons and OPCs involves paracrine signaling mechanisms—including brain-derived neurotrophic factor (BDNF) (Geraghty et al. 2019), neuregulin (Makinodan et al. 2012), and endothelin (Swire et al. 2019)—and also occurs electrophysiologically through functional glutamatergic and GABAergic neuron-to-OPC synapses (Bergles et al. 2000, Káradóttir et al. 2005, Lin & Bergles 2004, Mount et al. 2019).

GLIOMAS

Glial malignancies, or gliomas, are the most common primary brain cancer in both children and adults. Gliomas represent a group of clinically and molecularly distinct entities, each of which is composed of cellularly heterogeneous malignant cells with cellular subpopulations that closely resemble astrocytes, oligodendrocytes, OPCs, and earlier neural stem cells (Filbin et al. 2018, Neftel et al. 2019, Patel et al. 2014, Venteicher et al. 2017). It is believed that a subpopulation of stem-like glioma stem cells, also called brain tumor–initiating cells, are the most important for overall tumor growth and resistance to current therapies (Chen et al. 2012, Singh et al. 2004). In some glial malignancies, the glioma stem cell most resembles an early neural stem cell, while in others this stem-like cellular subpopulation that is thought to drive malignant progression most resembles OPCs (Filbin et al. 2018, Neftel et al. 2019, Patel et al. 2014, Venteicher et al.

2017). The most aggressive forms of high-grade gliomas include glioblastoma, which occurs most frequently in the cerebral hemispheres, and diffuse midline gliomas, characterized by a mutation in genes encoding histone-3 (H3K27M-mutated diffuse midline gliomas), that occur in the thalamus, brainstem (also called diffuse intrinsic pontine glioma), and spinal cord (Louis et al. 2021). While historically referred to as astrocytomas, gliomas are not believed to arise from mature astrocytes. Many studies have implicated precursors in the oligodendroglial lineage—from OPCs to earlier precursor cell states—as the cell of origin for these heterogenous tumors (Alcantara Llaguno et al. 2015; Filbin et al. 2018; Galvao et al. 2014; Haag et al. 2021; Liu et al. 2011; Monje et al. 2011; Nagaraja et al. 2017, 2019; Wang et al. 2020). Gliomas tend to occur in particular locations within the nervous system at particular ages. In general, these aggressive gliomas that form throughout the life span tend to do so from more central, midline structures such as brainstem and thalamus in children outward to more diffuse cortical, subcortical, or basal ganglia structures in adults. This pattern overlaps with the developmental myelin program from brainstem and spinal cord in early development to the far reaches of the hemispheres well into adulthood (Dvorak et al. 2021, Kinney et al. 1988, Yakovlev & Lecours 1967). Concordant with an oligodendroglial lineage cell of origin for many forms of high-grade glioma is the observation that the spatiotemporal pattern of glioma incidence maps well onto the time and place of discrete waves of developmental myelination and the anatomical locations described to date for ongoing myelin plasticity during adulthood (for further discussion, see Filbin & Monje 2019).

Neuronal Activity Drives Glioma Growth

Given their molecular similarities to OPCs, it was postulated that glioma cells may similarly proliferate in response to neuronal activity. To this end, optogenetic stimulation of cortical projection neurons in mice that had been xenografted with human high-grade glioma cells demonstrated that neuronal activity increased tumor proliferation in a circuit-specific manner (Venkatesh et al. 2015). The influence of neurons on glioma growth is profound; coculture of patient-derived glioma cells with mixed neurons induces an approximate tenfold increase in glioma cell proliferation (Venkatesh et al. 2019). The importance of neuronal activity in driving glioma growth is not specific to aggressive, malignant high-grade gliomas. Optic nerve activity regulates both initiation and growth of low-grade gliomas of the optic pathway (Pan et al. 2021). Optic pathway gliomas occur commonly in the neurofibromatosis type 1 (NF1) tumor predisposition syndrome. A mouse model of NF1-associated optic pathway glioma, in which mice consistently develop tumors of the optic nerve and chiasm at a predictable postnatal age, was used to test the influence of retinal ganglion cell axonal activity in the optic nerve on tumor initiation, maintenance, and progression. Like the findings in models of high-grade glioma discussed above, optogenetic stimulation of the optic nerve increased growth of optic pathway gliomas. Conversely, mice that were reared in complete darkness to decrease visual experience and reduce optic nerve activity just prior to the onset of optic pathway glioma formation did not develop optic pathway gliomas, compared to tumor development in all littermate mice raised in normal light cycles (Pan et al. 2021). Decreasing visual experience at the time of or just after optic pathway glioma formation resulted in far fewer and much smaller tumors compared to littermate control mice with normal visual experience, indicating a role for optic nerve activity in tumor initiation, maintenance, and growth (Pan et al. 2021).

Activity-Regulated Paracrine Factors

Activity-regulated secreted paracrine factors found in acute cortical slice conditioned medium promote glioma cell proliferation in a wide array of adult and pediatric high-grade glioma subtypes, including IDH-wild-type adult glioblastoma, IDH-mutant adult oligodendroglioma,

histone wild-type pediatric cortical glioblastoma, and H3K27M+ diffuse midline gliomas (Venkatesh et al. 2015). Similarly, factors secreted from retinal and optic nerve explants promote the proliferation of NF1-associated low-grade glioma cells (Pan et al. 2021). These activity-regulated paracrine factors driving glioma proliferation include BDNF and a shed form of neurologin-3 (NLGN3) (Pan et al. 2021; Venkatesh et al. 2015). NLGN3—a postsynaptic adhesion molecule present at both glutamatergic and GABAergic synapses (Südhof 2008)—was a surprising glioma mitogen, given that it was not previously known to be a mitogen in any context nor to be secreted. However, NLGN3 was found to be shed in the healthy brain in a strictly activity-regulated manner by the sheddase ADAM10 (Venkatesh et al. 2017). In the optic nerve, NLGN3 shedding was aberrantly increased in the context of NF1, suggesting that one component of the genetic predisposition to optic glioma formation reflects effects of NF1 mutation on retinal ganglion cells and other components of the optic nerve with respect to regulation of NLGN3 shedding (Pan et al. 2021). Interestingly, NLGN3 is expressed in both postsynaptic neurons and postsynaptic OPCs, and OPCs were found to be a major source of activity-regulated NLGN3 shedding (Venkatesh et al. 2017). OPCs are postulated to be the chief source of shed NLGN3 in the optic nerve (Pan et al. 2021). The role that NLGN3 plays in normal OPC physiology is incompletely understood but may reveal a missing link in paracrine signaling mechanisms between active neurons and neighboring OPCs upstream of adaptive myelination.

Shed Neuroligin-3 Signaling

To test the relative contribution of NLGN3 to glioma pathophysiology, patient-derived high-grade glioma xenografts were implanted into the environment of NLGN3 wild-type or knockout mouse brain. Quite surprisingly, a wide range of patient-derived high-grade glioma xenografts failed to grow in the absence of microenvironmental NLGN3 (Venkatesh et al. 2017). Optic pathway glioma initiation and growth also depends on NLGN3 signaling, as NLGN3 knockout prevents optic pathway glioma formation in mice (Pan et al. 2021). In contrast to the central role of NLGN3 in glioma pathophysiology, growth of a patient-derived xenograft model of breast cancer brain metastasis did not depend on NLGN3 in the microenvironment, suggesting that while NLGN3 emerges as an unexpected dependency across glial malignancies, it is not a critical mechanism in all forms of brain cancer. Treatment with an ADAM10 inhibitor in clinical development, used previously in clinical trials for breast cancer (Newton et al. 2010), blocked glioma progression in patient-derived orthotopic xenograft models (Venkatesh et al. 2017). Similarly, ADAM10 inhibition prevented glioma progression in the genetically engineered mouse model of NF1-associated optic pathway glioma discussed above (Pan et al. 2021). ADAM10 inhibitor therapy is presently in an early-phase clinical trial for children with high-grade gliomas (NCT04295759).

NLGN3 signals through a still unknown binding partner on glioma cells. Phosphoproteomic studies revealed that when NLGN3 binds to the glioma cell, this activates focal adhesion kinase and downstream PI3K-mTOR, SRC, and RAS pathways (Venkatesh et al. 2017). While this recruitment of multiple oncogenic signaling pathways explains the sufficiency of NLGN3 in promoting malignant glioma cell proliferation, it does not explain the unexpected dependency. Further studies revealed that NLGN3 promotes prominent gene expression changes in the glioma cell, including a feed-forward upregulation of *NLGN3* itself (Pan et al. 2021; Venkatesh et al. 2015, 2017), together with upregulation of a number of other synapse-associated genes (Venkatesh et al. 2017). *NLGN3* gene expression levels inversely correlate with overall patient survival in adult glioblastoma (Venkatesh et al. 2015), underscoring the clinical relevance of NLGN3 signaling and neuron-glioma interactions in general.

Neurotrophin Signaling

Neurotrophins are a group of growth factors that have important roles in nervous system cell survival, proliferation, or differentiation from neural or glial precursors into more mature cells. The main neurotrophins are nerve growth factor (NGF), BDNF, NT-3, and NT-4, and their binding partners are either the p75 or tropomyosin receptor (Trk) family (Huang & Reichardt 2001). Neurotrophins are important not only for developing neurons and for neurogenesis in adulthood but also for glial cells, particularly OPCs. NT-3 was shown to be a critical neurotrophin for proliferation of OPCs in vitro and in vivo (Barres et al. 1994). Similarly, BDNF signaling through TrkB receptors on OPCs regulates myelin development (Wong et al. 2013) and is required for activity-dependent myelination of cortical projection neurons (Geraghty et al. 2019). One role for BDNF in OPCs is to increase glutamate responsivity (Lundgaard et al. 2013), although the role of glutamatergic signaling in activity-regulated myelination remains to be fully understood (Monje & Káradóttir 2021).

Gliomas can express BDNF, NGF, NT-3, and receptors p75, TrkB, and TrkC, highlighting the potential of neurotrophins for autocrine glioma growth (Johnston et al. 2007, Lawn et al. 2015). We highlight what is known for BDNF since it is the most well studied. As mentioned, BDNF was found to be an activity-dependent secreted mitogen involved in the proliferation of both high-grade and low-grade gliomas (Pan et al. 2021, Venkatesh et al. 2015). The effects of BDNF on glioma cells depend on which form of BDNF is responsible for the signaling. ProBDNF, the precursor to mature BDNF that binds to p75 receptor, inhibits growth of adult glioblastoma cells in vitro (Xiong et al. 2013b). Conversely, mature BDNF, which binds to the receptor TrkB, increases growth of glioblastoma cells in vitro (Xiong et al. 2013a). Glioma stem cells express TrkB receptors and receive BDNF signaling from neighboring more differentiated glioma cells to continually drive growth of the glioma stem cell population in adult glioblastoma (Wang et al. 2018). Mature BDNF and TrkB receptor expression levels in adult human glioma specimens also correlate with degree of malignancy (Xiong et al. 2015). In the healthy nervous system, BDNF plays diverse roles in development and plasticity of synaptic connectivity and synaptic strength (for review, see Park & Poo 2013). Whether BDNF acts as more than a mitogen in gliomas remains to be elucidated, but recent insights into the synaptic physiology of brain cancers, discussed below, raise questions about the many ways in which BDNF and other neurotrophins may contribute to cancer pathophysiology.

Electrochemical and Synaptic Signaling

A body of evidence is now emerging that gliomas integrate synaptically and electrically into neural circuits (**Figure 1**), building upon early work demonstrating glioma cell responsivity to glutamate (Ishiuchi et al. 2002, Labrakakis et al. 1998a). Given the functional similarities between glioma cells and OPCs, which form synapses with neurons (Bergles et al. 2000, Káradóttir et al. 2005), it was postulated that gliomas could be integrating into neural networks by generation of bona fide synapses with neurons. Two groups independently discovered that neuron-to-glioma synapses form in a subpopulation of glioma cells within both adult and pediatric types of high-grade glioma (Venkataramani et al. 2019, Venkatesh et al. 2019). Clear synaptic structures are seen in primary tumor tissue and in patient-derived glioma xenograft tissue, using immuno-electron microscopy to unambiguously label glioma cells (Venkataramani et al. 2019, Venkatesh et al. 2019). Patch-clamp electrophysiological recordings of high-grade glioma cells, either in hippocampal slices from xenografts or in cocultures with neurons, demonstrated fast (<5 ms) postsynaptic currents that were both spontaneously occurring and evoked by neuronal stimulation and that were blocked by tetrodotoxin and NBQX [an antagonist to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors] but not antagonists to NMDA receptors. Adult and

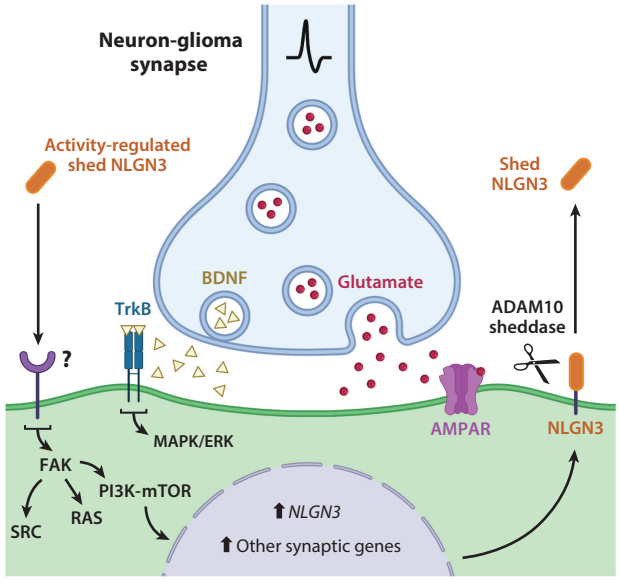

Figure 1

Neural signaling in gliomas. Neuronal activity results in paracrine and synaptic signaling to glioma cells. Activity-regulated shedding of neuroligin-3 (NLGN3, *orange*) from synapses in the tumor microenvironment results in NLGN3 binding to an as-of-yet unknown binding partner (*dark purple*) on glioma cells, which stimulates oncogenic signaling pathways, including focal adhesion kinase (FAK) and downstream SRC, RAS, and PI3K-mTOR pathways. This results in cell proliferation and leads to expression of NLGN3 and other synaptic genes in the glioma cell. NLGN3 promotes synaptogenesis and is also shed from the glioma cell surface by the sheddase ADAM10 (*scissors*). AMPA receptor (AMPAR, *magenta*)-mediated electrochemical synapses form between neurons and glioma cells. AMPAR-mediated depolarization in glioma cells drives tumor growth through voltage-sensitive mechanisms. Neuronal activity-regulated BDNF (*yellow triangles*) signaling to the BDNF receptor TrkB (*blue*) on glioma cells, with consequent stimulation of the MAPK/ERK pathway, is an additional paracrine factor promoting glioma proliferation. Glutamate is shown as red circles. Figure adapted from image created with BioRender.com.

pediatric high-grade gliomas express under-edited GluA2 AMPA receptor subunits, rendering these neuron-to-glioma AMPA receptor-mediated synapses calcium permeable (Venkataramani et al. 2019, Venkatesh et al. 2019). These currents, occurring in about 5–10% of glioma cells within each tumor examined, exhibited multiple electrophysiological characteristics of synaptic currents, including paired pulse facilitation and miniature excitatory postsynaptic currents in the presence of strontium (Venkataramani et al. 2019, Venkatesh et al. 2019). A second type of inward current was found in each tumor, evident in as many as 60% of malignant cells in some patient-derived models, that exhibited markedly slower (>1 s) kinetics. This prolonged current was found to represent a nonsynaptic, potassium-evoked current and was also dependent on neuronal activity (Venkataramani et al. 2020, Venkatesh et al. 2019). These prolonged, potassium-evoked currents are reminiscent of activity-dependent, slow inward potassium currents found in normal astrocytes (Kuffler 1967, Sibille et al. 2014) and some OPCs (Spitzer et al. 2019). As these prolonged currents depend on action potential–dependent increases in extracellular potassium, the glioma potassium-evoked current amplitude and duration were found to be proportionate to the activity of local neurons and scale with field potential (Venkatesh et al. 2019). These potassium-evoked currents are amplified through gap junctional coupling between glioma cells (Venkataramani et al. 2020, Venkatesh et al. 2019). Gap junctional blockade decreases the amplitude of these

potassium-evoked currents and also abrogates the synchrony of calcium transients propagating through the tumor in patient-derived glioma xenografts (Venkataramani et al. 2019, Venkatesh et al. 2019) and in patient-derived glioma transplants to human neocortical slice cultures (Schneider et al. 2021).

Given that glioma cells exhibit at least two mechanisms of membrane depolarization, and in light of the role that membrane depolarization plays in regulating normal neural stem/precursor cell proliferation as discussed above, it was hypothesized that membrane depolarization alone may promote glioma proliferation and growth. To test this idea, patient-derived glioma cells were engineered to express channelrhodopsin-2, xenografted to the mouse cortex, and then optogenetically depolarized in vivo. Optogenetic depolarization of glioma xenografts increases tumor cell proliferation through currently unknown voltage-sensitive downstream mechanisms (Venkatesh et al. 2019). The dependency of glioma growth on AMPA receptor signaling was demonstrated genetically by expression of a dominant-negative version of the GluA2 subunit in glioma cells, as well as pharmacologically using the AMPA receptor–blocking antiepileptic drug perampanel (Venkataramani et al. 2019, Venkatesh et al. 2019).

Glioma cells connect to each other over long distances via connexin-43-mediated gap junction–connected microtubes (**Figure 2*a***), and this glioma network formation is implicated as a considerable source of treatment resistance in glioblastoma (Osswald et al. 2015, Weil et al. 2017). Such microtubes have been found in adult glioblastoma (Osswald et al. 2015) and pediatric H3K27M+ diffuse midline gliomas (Nagaraja et al. 2019, Venkatesh et al. 2019) but are less prominent in IDH-mutated oligodendrogliomas (Osswald et al. 2015). Subsequent work showed a role for the membrane-associated protein tweety-homolog-1, which is important in neurodevelopment as a factor that causes extension of neurites (Stefaniuk et al. 2010), in the development of these invasive microtubes (Jung et al. 2017). Interestingly, exposure to neuronal activity-regulated secreted factors upregulates tweety-homolog-1 expression in glioma cells (Venkatesh et al. 2015), although the broader influence of neuronal activity on microtube elaboration remains to be fully established. In adult glioblastoma, neuron-to-glioma synapses were chiefly found on tumor microtubes, suggesting that neuron-glioma networks could involve long-range connections between distant glioma cells (Venkataramani et al. 2019). While neuron-to-glioma synaptic structures were found on a relatively small subset of total glioma cells, this gap junction–coupled mechanism suggests that large networks of glioma cells could be activated from a small number of synaptic connections, or from a subset of glioma cells sensing activity-dependent changes in extracellular potassium. Underscoring the functional importance of such gap junctional coupling, the gap junction inhibitor meclofenamate, which decouples the synchrony of glioma network calcium transients (Schneider et al. 2021, Venkataramani et al. 2019, Venkatesh et al. 2019), reduces glioma growth in vivo (Venkatesh et al. 2019). It remains to be determined whether microtubes and gap junction–coupling or neuron-to-glioma synapses are present in low-grade gliomas.

Single-cell transcriptomic studies of primary glioma biopsy samples demonstrated that synapse-associated genes, especially AMPA receptor subunit genes, are robustly expressed in malignant cells (Venkataramani et al. 2019, Venkatesh et al. 2019). Examining each patient tumor, it is unsurprisingly the OPC-like subset of malignant cells that exhibit the strongest synaptic gene enrichment (Venkatesh et al. 2019). As noted above, NLGN3 signaling increases synaptic gene expression in glioma cells (Venkatesh et al. 2017), including gene and protein expression of NLGN3 itself (Venkatesh et al. 2015), which localizes to the glioma cell membrane and can also be shed by glioma cells in an ADAM10-dependent manner (Venkatesh et al. 2017) (**Figure 1**). Nonneuronal cells engineered to express neuroligin will induce presynaptic structural changes in adjacent neurons (Scheiffele et al. 2000). Taken together, these observations suggest that NLGN3 may function

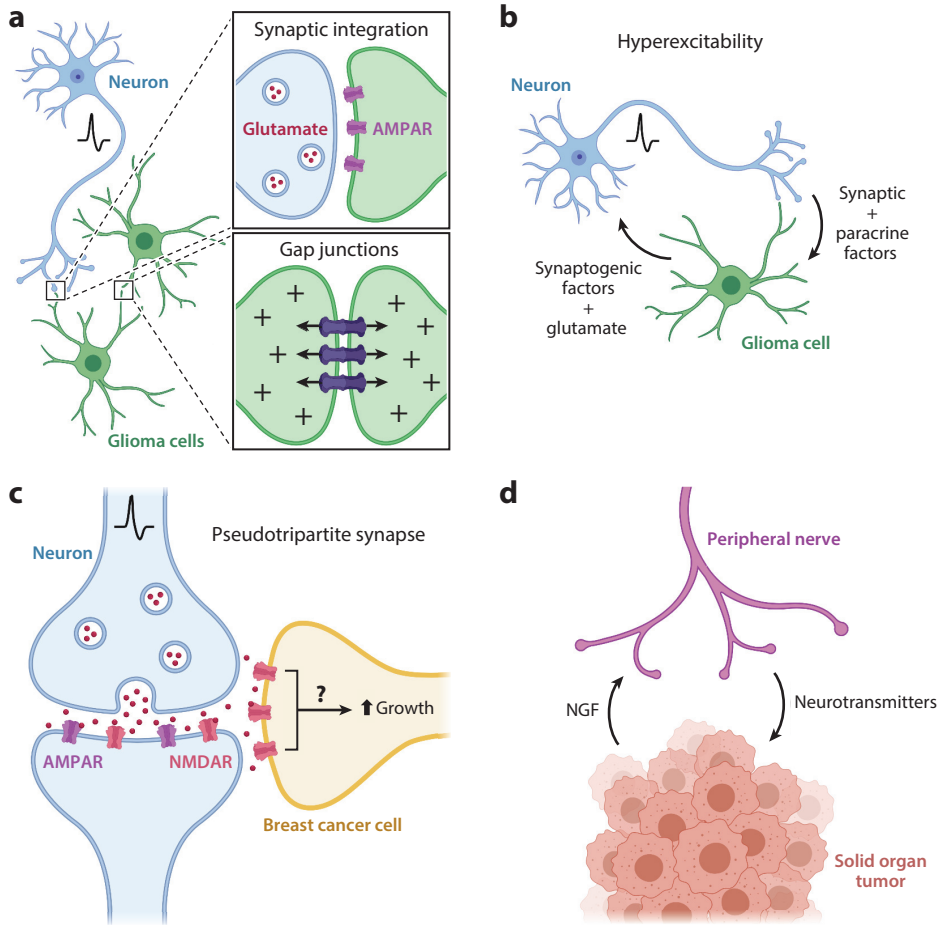

Figure 2

Examples of nervous system–cancer cross talk in the brain and body. (*a*) Neurons (*blue*) form AMPA receptor (AMPAR, *magenta*)-dependent glutamatergic synapses with glioma cells (*green*), and glioma cells are coupled to each other through connexin-43-mediated gap junctions (*dark purple*) and tumor microtube networks. (*b*) Glioma cells secrete synaptogenic factors and glutamate, which causes neuronal hyperexcitability, resulting in a feed-forward malignant loop driving paracrine and synaptic neuron-glioma interactions. (*c*) Breast cancer cells (*yellow*) metastatic to brain express NMDA receptors (NMDARs, *red*) and integrate perisynaptically in pseudotripartite synapses to exploit synaptic glutamatergic (*red circles*) transmission between neurons. Currently unknown NMDA-mediated signaling mechanisms drive breast cancer metastasis growth in the brain. (*d*) Many solid organ tumors (*pink*) of the body secrete neurotrophins, such as nerve growth factor (NGF), to increase peripheral nerve (*magenta*) branching into the tumor microenvironment, while nerve-derived neurotransmitter signaling regulates tumor growth. Figure adapted from image created with BioRender.com.

to promote neuron-to-glioma synaptogenesis. This idea was tested by coculturing patient-derived glioma cells together with either wild-type or NLGN3 knockout neurons. Indeed, fewer neuron-to-glioma synaptic structures formed in the absence of microenvironmental NLGN3 (Venkatesh et al. 2019), indicating that one key effect of shed NLGN3 in the tumor microenvironment is to promote malignant synaptogenesis.

Whether other types of synapses exist in gliomas remains to be determined, but it is clear that glioma cells express a range of neurotransmitter receptors and that various neurotransmitters can

signal to glioma cells. Whether different types of gliomas respond heterogeneously to the various neurotransmitters secreted throughout the nervous system also remains to be determined, and most studies have been performed to date in models of adult glioblastoma. In a mouse model of glioblastoma and human glioblastoma cell lines, GABA signaling through the $GABA_A$ receptor results in an inward chloride current, glioma cell hyperpolarization, and inhibition of tumor growth (Blanchart et al. 2017). Concordantly, optogenetic stimulation of GABAergic interneurons reduces growth in a murine allograft model of adult glioblastoma (Tantillo et al. 2020). As the intracellular chloride concentration determines whether GABA signaling results in inward or outward chloride currents, one could imagine an opposite effect in glioma types that more closely resemble neural precursor cells or OPCs, which exhibit depolarizing chloride efflux in response to GABA (Lin & Bergles 2004). Underscoring heterogeneity in the response of adult glioma cells to GABA, another study found GABA-induced currents in oligodendrogliomas and lower-grade astrocytomas, but the direction of current (inward, hyperpolarizing or outward, depolarizing) varied across cells within a given tumor (Labrakakis et al. 1998b). Molecularly defined, tumor type–specific effects of GABA remain to be fully explored. As for other neurotransmitters, tumor growth or invasion-promoting roles have been described for serotonin (Kast 2010, Tsuchioka et al. 2008), dopamine (Bhat et al. 2020, Caragher et al. 2019, Dolma et al. 2016), acetylcholine (Thompson & Sontheimer 2019), and catecholamine (He et al. 2017, Tewarie et al. 2021) signaling in adult glioblastoma. Whether these neurotransmitters exert effects in a paracrine or synaptic manner and whether there are tumor type–specific differences in neurotransmitter responses are unexplored questions that await further study.

Axon Pathfinding Signals

Signaling pathways classically involved in axonogenesis, axon pathfinding, and other processes of nervous system patterning have been widely implicated in cancer pathogenesis (for review, see Mehlen et al. 2011). We focus here on axon pathfinding signals in gliomas, given the characteristically infiltrative behavior of glioma cells together with the newly recognized propensity of high-grade gliomas to form long subcellular microtubes that connect malignant cells in a dispersed, gap junction–coupled network (Osswald et al. 2015). Underscoring the principle that mechanisms of neurodevelopment are recapitulated in nervous system cancers, Ephrin-Eph receptor signaling has been found to promote tumor cell invasion in adult glioblastoma (Miao et al. 2015; Nakada et al. 2004, 2006) and in H3K27M+ diffuse midline glioma (Nagaraja et al. 2017). Pleiotrophin is a molecule that promotes neurite outgrowth and neuroblast migration in the healthy brain (Li et al. 1990, Maeda & Noda 1998, Rauvala & Pihlaskari 1987) and also promotes glioma migration (Lu et al. 2005, Ulbricht et al. 2003). Pleiotrophin is secreted by stem cells in the subventricular zone and serves as a chemoattractant to promote the insidious propensity for gliomas to spread to subventricular stem cell niches (Qin et al. 2017). Semaphorin-neuropilin signaling has also been implicated in glioblastoma invasion, with adult human glioblastoma cultures demonstrating expression of semaphorins SEMA3A and SEMA3C together with plexins and neuropilins, the receptors for semaphorins (Rieger et al. 2003). SEMA3A-neuropilin1 signaling promotes glioblastoma cell invasion (Bagci et al. 2009). Slit-Robo signaling, a classically repulsive cue, may be at play in gliomas as well. Expression of Robo1 was found in a subset of human gliomas, and Robo1-expressing glioma cell lines exhibited migration away from Slit2 in a directional in vitro assay (Mertsch et al. 2008). Slit2 is expressed at low levels and with inverse correlation to tumor grade (Mertsch et al. 2008). Concordantly, overexpression of Slit2 in glioma cells decreases glioblastoma invasion in a mouse model, creating well-circumscribed nodular tumors rather than the typical patterns of diffusely invasive growth (Yiin et al. 2009).

Glioma-Induced Neuronal Hyperexcitability and Neural Circuit Remodeling

Just as excitatory neuronal activity promotes glioma progression, both pediatric and adult high-grade gliomas exert profound influences on neuronal excitability (Buckingham et al. 2011; Campbell et al. 2012, 2015; Lin et al. 2017; Venkatesh et al. 2019; Yu et al. 2020), thereby establishing a malignant cycle that drives tumor progression (**Figure 2*b***). Neuronal hyperexcitability has been described not only in glioma preclinical models but also in human patients. Intraoperative electrocorticography prior to initial resection in awake, resting adults demonstrated hyperexcitability in glioma-infiltrated brain compared to more normal-appearing cortex, illustrating that this hyperexcitability is present even at the time of initial diagnosis (Venkatesh et al. 2019). Indeed, seizures commonly occur in patients with gliomas, and in many cases are the initial presenting problem that leads to the diagnosis of brain cancer in an otherwise asymptomatic patient. Studies in xenograft models as well as human patients undergoing surgical resection have demonstrated that for tumors with a nodular core and invasive edge such as glioblastoma, the area of maximal epileptiform activity occurs at the border zone between expanding tumor and normal brain; microdialysis sampling of this border zone reveals increased glutamate concentrations relative to the tumor core (Köhling et al. 2006, Marcus et al. 2010). Patient-derived xenograft models of adult glioblastoma exhibit nonsynaptic secretion of glutamate through the x_c^- glutamate-cysteine exchanger (*SLC7A11*) (Buckingham et al. 2011), and this excess glutamate contributes to cortical hyperexcitability and seizures (Campbell et al. 2012). Disinhibition due to specific loss of GABAergic interneurons in the tumor microenvironment also contributes to glioma-associated neuronal hyperexcitability (Campbell et al. 2015). The mechanisms by which gliomas induce a loss of interneurons remain to be determined. Even more enigmatic is the finding that glioblastomas can induce impairment of neuronal KCC2 cotransporter activity, increasing neuronal intracellular chloride concentration and rendering mature neurons excitable by GABA (Campbell et al. 2015). A third mechanism by which glioma cells increase neuronal excitability is through secretion of synaptogenic factors by a subpopulation of astrocyte-like glioma cells (Lin et al. 2017). Fascinatingly, distinct point mutations in the *PIK3CA* oncogene (encoding PI3K) in genetic mouse models of glioblastoma result in differential induction of neuronal hyperexcitability through malignant cell secretion of the synaptogenic factor glypican-3 (Yu et al. 2020). This indicates that variants of an oncogene may selectively regulate this synaptogenic subpopulation of astrocyte-like glioma cells and differentially cause glioma-associated neuronal hyperexcitability and seizures. Such intertumoral heterogeneity suggests that molecular characteristics of the tumor may cause varying degrees of neuronal synaptogenesis and possibly varying degrees of synaptic integration of glioma into neural circuits. How this glioma cell-derived synaptogenic factor secretion influences neuron-to-glioma synaptic connectivity is not yet clear. However, emerging work indicates that glioma-derived synaptogenic factors contribute to functional remodeling of neural circuits in humans, including language circuitry in patients with left hemispheric glioblastoma (Krishna et al. 2021a). Intraoperative electrocorticography and magnetic electroencephalography in adult patients indicate geographic regions within a glioblastoma that exhibit differentially high functional connectivity with normal brain as well as heterogeneity in the degree of functional connectivity between patients. These regions of higher functional connectivity contain glioma cells that are more responsive to neuronal signals and are more synaptogenic, exhibiting greater secretion of the classical synaptogenic factor thrombospondin-1. High functional connectivity between glioblastoma cells and normal brain robustly correlates with poor survival (Krishna et al. 2021a), underscoring the pathophysiological significance of glioma integration into neural circuits. Functional MRI (fMRI) has also been used to explore network changes in patients with low- and high-grade gliomas, demonstrating fMRI changes not only in the ipsilateral tumor-infiltrated cortex

but also in contralateral, normal-appearing brain, further illustrating broad effects of the tumor on neural circuit function. The observed disruption in resting-state fMRI connectivity increases with increasing tumor grade and correlates with degree of cognitive symptoms (Stoecklein et al. 2020). The effects of bidirectional neuron-glioma signaling on neurological function and patient quality of life are an important area of research in the emerging field of cancer neuroscience, and much remains to be learned from a systems neuroscience perspective (Krishna et al. 2021b).

NONGLIAL NEURAL CANCERS

A great deal remains to be learned about interactions between neural cancers and the nervous system. The influences of the nervous system on nonglial primary neural tumors, including malignancies that arise from and resemble neuronal precursors, are largely unknown. Given the diverse influences that neural signaling exerts in various neural precursor cell populations discussed above, neural signaling effects may play heterogenous roles in brain tumors such as medulloblastoma—a neuroblast-like cancer of the cerebellum—and other neuroectodermal tumors. In this regard, neural signaling may alternatively promote proliferation or differentiation, likely predicted by the effects on the cell of origin for each cancer entity. Early studies indicate powerful influences of neural signaling on these nonglial, chiefly pediatric neural cancers. For example, NLGN3 promotes proliferation of neuroblastoma—the peripheral, neural crest–derived tumor that typically occurs in infants and young children—through stimulation of PI3K signaling (Li et al. 2019), similar to the effects in gliomas described above (Venkatesh et al. 2015, 2017). Conversely, neurotrophin signaling through TrkA receptors may limit growth, as TrkA expression levels correlate with improved outcomes in neuroblastoma (Nakagawara et al. 1993, Suzuki et al. 1993). Similarly, neurotrophin signaling through TrkC may limit the growth of medulloblastoma (Segal et al. 1994).

BRAIN METASTASES

Increasing evidence indicates that tumors metastatic to the brain are also robustly regulated by interactions with neural cells. While a diverse array of tumor types metastasize to the brain, and are each likely to exhibit disease-specific mechanisms, common principles are emerging for cancers with a high propensity for brain metastasis, including breast and lung cancers. Once inside the brain parenchyma, many metastatic cancer cells fail to grow within the brain microenvironment (Kienast et al. 2010). This finding suggested that metastatic tumor cells that successfully colonize the brain and establish a tumor mass might have adapted specific mechanisms to thrive in the brain parenchymal niche. Astrocytes, which outnumber neurons by a ratio of 10:1, play a central role in establishing brain metastases. Breast and lung metastases to brain express protocadherin-7, which enables the formation of connexin-43-mediated gap junctions with astrocytes. This carcinoma-astrocyte gap junctional coupling enables transfer of the second messenger cGAMP to astrocytes, stimulating the cGAS-STING pathway and increasing cytokine (IFNa, TNF) production by astrocytes, which in turn supports metastasis growth through paracrine signaling (Chen et al. 2016). Like the effect of gap junctional blockade described above in glioma, gap junctional blockade with meclofenamate decreased the progression of breast and lung cancer brain metastases in mouse models (Chen et al. 2016).

Further elucidating key interactions of metastatic cells with neural cells, a recent study demonstrated that breast cancer cells express NMDA receptors and form pseudotripartite synapses (**Figure 2*c***) at the synaptic cleft between two neurons to enable glutamatergic signaling in a paracrine, perisynaptic fashion (Zeng et al. 2019). Electron microscopy and electrophysiological studies demonstrated that breast cancer cells metastatic to brain assume the perisynaptic position that is normally occupied by astrocytes (Zeng et al. 2019). What happens to the normal

astrocyte process to enable replacement by the breast cancer cell remains to be determined. Interestingly, normal astrocytes express neuroligins that interact with presynaptic neuronal neurexins to facilitate the normal tripartite synaptic structure (Stogsdill et al. 2017). Whether neuroligins are expressed by breast cancer brain metastatic cells and whether these or other synaptic adhesion molecules play a role in establishing neuron–cancer cell synaptic structures remain to be determined. It is currently unknown whether lung cancer metastases use tripartite synapses as part of their means of colonization and growth in the brain parenchyma, but there is reason to suspect that such interactions could be at play. NMDA receptor subunits are expressed in lung adenocarcinoma cancer cells in vitro, and treatment with the NMDA receptor antagonist dizocilpine suppressed growth of cells in vitro by modulation of the ERK pathway (Stepulak et al. 2005). Other neurotransmitters may also influence the progression of brain metastases. For example, breast cancer cells upregulate GABA receptors once metastasized to the brain and proliferate in a dose-dependent fashion in response to exogenous GABA (Neman et al. 2014).

PERIPHERAL NERVES AND SOLID ORGAN TUMORS

The peripheral nervous system, composed of the sensory, motor, autonomic, and enteric components—branching as extensively as the circulatory system throughout the body—influences tissue development, homeostasis, and regeneration. Similar to the central nervous system, neuronal activity robustly regulates tissue stem and precursor cell populations in a diverse array of organs. For example, parasympathetic innervation of the nascent salivary gland, signaling through muscarinic receptors on epithelial progenitor cells, is required for proper organ development (Knox et al. 2010) and promotes salivary gland regeneration after injury (Knox et al. 2013). Similarly, in the developing skin, peripheral nerves and Schwann cells coordinate arterial branch distribution and growth during dermal organogenesis through a mechanism requiring VEGF (Mukouyama et al. 2002).

Parallel to this role of innervation in development is an emerging role of innervation in a range of solid tumors of the body. Tumor cell migration along nerves—called perineural invasion—has long been associated with worse prognosis in a variety of cancers (Liebig et al. 2009). This may not simply reflect aggressive metastatic properties inherent to the cancer itself, as perineural invasion has been observed in the absence of ongoing lymphatic or hematogenous spread. These observations suggested a role for cross talk between nerves and tumor cells in cancer pathogenesis. Indeed, mounting evidence implicates nervous system regulation of cancers of the prostate (Magnon et al. 2013, Zahalka et al. 2017), stomach (Hayakawa et al. 2017, Zhao et al. 2014), skin (Peterson et al. 2015), pancreas (Renz et al. 2018a,b), and breast (Sloan et al. 2010). A landmark study from the Frenette group (Magnon et al. 2013) demonstrated that sympathetic nerve fibers in the prostate gland drive initiation and progression of prostate cancer through beta-2 and beta-3 adrenergic receptor signaling, while parasympathetic nerves promote prostate cancer spread. Further work from the same group demonstrated that adrenergic signaling also induces an angiogenic state in endothelial cells of the tumor microenvironment that further promotes prostate tumor growth (Zahalka et al. 2017). Cholinergic innervation similarly promotes tumor initiation and growth in the stomach, and denervation of the stomach markedly reduces tumor formation and growth in preclinical cancer models (Hayakawa et al. 2017, Zhao et al. 2014). In contrast to this growth-promoting role of cholinergic signaling in prostate and stomach cancer, in pancreatic cancer cholinergic signaling suppresses tumor progression (Renz et al. 2018b). However, this is not to suggest that innervation does not play a central role in pancreatic cancer growth. Pain is an early symptom of pancreatic cancer, and concordantly, aberrantly increased pancreatic innervation precedes the transition from preneoplastic lesions to fully transformed pancreatic

cancer (Stopczynski et al. 2014), and pancreatic innervation by sensory (Saloman et al. 2016) and adrenergic (Renz et al. 2018a) nerves drives pancreatic cancer growth. Adrenergic signaling in cancer can result from either tumor-associated adrenergic nerves or circulating catecholamines (Cui et al. 2019, Sloan et al. 2010). Regardless of source, it is possible that systemic adrenergic receptor blockade may confer some therapeutic benefit, as supported by retrospective studies in humans with pancreatic cancer (Renz et al. 2018a). Prospective clinical trials targeting adrenergic signaling in pancreatic and breast cancers are underway (Hiller et al. 2020) (e.g., NCT01847001, NCT03838029, NCT00502684).

In some cancers, neurotransmitter signaling emerges not from nerves in the tumor microenvironment but from the cancer cells themselves, such as glutamatergic signaling in an autocrine fashion. In a mouse model of pancreatic neuroendocrine tumors, NMDA receptors were found at the invasive tumor front, and glutamate secreted from tumor cells themselves increased tumor proliferation and invasiveness through a mechanism involving the cytoplasmic adaptor protein GKAP (Li & Hanahan 2013, Li et al. 2018).

The feed-forward cycle of neuron-induced tumor growth and tumor-derived nervous system remodeling described above in brain cancer is recapitulated in peripheral cancers as well. Cancer cells induce axonogenesis into the tumor microenvironment (Ayala et al. 2001) through secretion of neurotrophins such as NGF (Hayakawa et al. 2017, Pundavela et al. 2015), thereby amplifying this cycle of nerve-cancer cross talk (**Figure 2*d***). In an unexpected mechanism, remodeling of the neural tumor microenvironment can also come from central nervous system–derived neural precursor cells. In a mouse model of prostate cancer, subventricular zone neuroblasts were found to migrate out of the central nervous system and into the prostate from a hematogenous route to initiate local neurogenesis in the tumor microenvironment (Mauffrey et al. 2019).

CONCLUSIONS

As mechanisms of neural signaling in cancer come to light, new therapeutic strategies are beginning to emerge that may complement more traditional cancer treatments. While much remains to be learned, the emerging field of cancer neuroscience holds great promise for improved outlooks in seemingly intractable diseases like glioblastoma and pancreatic cancer. We may, in turn, learn a great deal about the neural regulation of normal development and plasticity through the magnified lens of cancer.

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