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Review

Neurons as stromal drivers of nervous system cancer formation and progression

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SUMMARY

Similar to their pivotal roles in nervous system development, neurons have emerged as critical regulators of cancer initiation, maintenance, and progression. Focusing on nervous system tumors, we describe the normal relationships between neurons and other cell types relevant to normal nerve function, and discuss how disruptions of these interactions promote tumor evolution, focusing on electrical (gap junctions) and chemical (synaptic) coupling, as well as the establishment of new paracrine relationships. We also review how neuron–tumor communication contributes to some of the complications of cancer, including neuropathy, chemobrain, seizures, and pain. Finally, we consider the implications of cancer neuroscience in establishing risk for tumor penetrance and in the design of future anti-tumoral treatments.

INTRODUCTION

Cancers initiate, evolve, and progress within a local environment rich in non-neoplastic cells, which largely reflect the normal cellular constituency of their surrounding tissue milieu. The non-neoplastic cells in these tumor microenvironments contain immune system cells (T and B lymphocytes, monocytes, and mast cells), fibroblasts, and vascular elements, which communicate with the cancer cells to regulate overall tumor fitness, as well as contribute to the ability of cancers to evade conventional and targeted therapies.[1–3] Although considerable research has focused on cancer-associated fibroblasts,[4,5] immune cells,[6–9] and endothelial cells,[10,11] until recently, comparatively less emphasis has been placed on the role of nerve cells (neurons) in the pathogenesis of cancer.[12]

The idea that neurons might participate in cancer pathogenesis originated with Hans Scherer in the 1930s, who first described invasive brain cancer cells encircling neuronal cell bodies and dendrites.[13,14] This characteristic cell grouping, known as ''perineuronal satellitosis,'' mirrors the clustering of macroglia (astrocytes and oligodendrocytes) around neurons in the healthy nervous system, as originally reported in 1899 by Santiago Ramon y Cajal, raising the intriguing possibility that a symbiotic relationship exists between glial and neuronal elements in both health and disease.[15] Importantly, this association is not unique to the nervous system neoplasias, but is also observed in cancers outside of the brain, where perineural invasion of tumor cells is a common feature associated with poor prognosis in pancreatic ductal adenocarcinoma, gastric carcinoma, colorectal cancer, prostate cancer, head and neck cancer, biliary tract tumor, and cervical cancer.[16–23]

With the recognition that neurons commonly integrate into most solid tumors and that neuron-glial relationships exist even in the absence of disease, it becomes increasingly important to consider neuronal contributions to cancer as an extension of their homeostatic and adaptive roles in the development and maintenance of the healthy body. In this review, we focus on nervous system tumors and discuss how these cancers usurp normal neuronal interactions to facilitate tumor initiation, maintenance, and progression.

NEURONS INTERACT WITH OTHER CELL TYPES DURING NERVOUS SYSTEM DEVELOPMENT AND HOMEOSTASIS

Neurons are first born during embryonic brain development,[24–26] when they begin to instruct the proliferation, differentiation, and specification of the central nervous system (CNS)[27] through interactions with oligodendrocyte lineage cells, astrocytes, microglia, and T lymphocytes (Figure 1). One of the major mechanisms by which neurons control CNS development is through their electrical activity. In this regard, neuronal activity is critical for neural induction, neural stem cell and precursor cell proliferation, migration and differentiation, synaptogenesis, oligodendrogenesis, and myelination.[28] As such, productive associations with oligodendrocyte precursor cells (OPCs) are critical for proper myelination and function of neurons,[29–32] whereas crosstalk with astrocytes helps dictate neuronal synapse formation, function, and elimination.[33–39] Similarly, neuron-secreted neurotransmitters depolarize neural progenitors to inhibit DNA synthesis during development, as well as induce neurogenesis in the adult brain.[27,40,41] Moreover, neurons in the peripheral nervous system (PNS) interact with macroglia (Schwann cells) to control their proliferation and survival and influence their own myelination.[42,43]

Neurons can additionally interact with immune system cells, such as resident brain macrophages (microglia).[44–46] Neuronal activity regulates microglia phagocytosis to selectively eliminate synapses during development (synaptic pruning),[47,48] a process that strengthens the remaining neuronal circuits. Neurons also communicate with T lymphocytes, which in turn, change the function of other cells in the healthy CNS[49] to influence learning

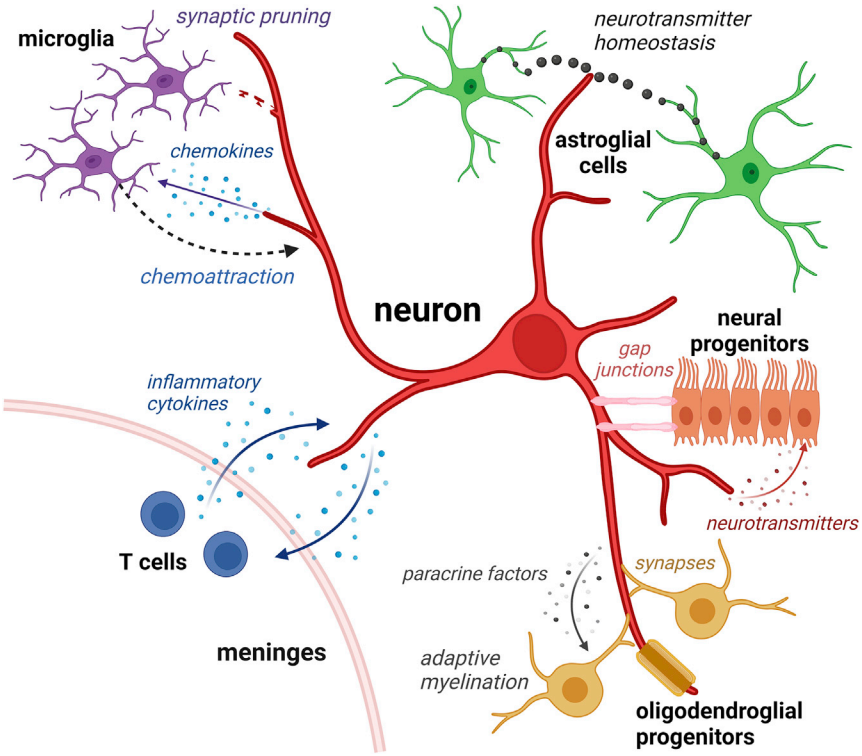

Figure 1. Neurons interact with numerous cell types during nervous system development and maintenance

Neurons in the central nervous system interact with microglia through chemokine attraction (chemoattraction) to enable synaptic pruning and induce neuroplasticity, but can also communicate with T cells in the meningeal spaces to modify neuronal function and behavior. In addition, neurons form cooperative relationships with astroglial cells (neurotransmitters), neural progenitors (gap junctions), and oligodendrocyte precursors (OPCs, direct synapses, neurotransmitters) to regulate neuroglial function, neurogenesis, and adaptive myelination. Similar interactions also occur in the peripheral nervous system between immune system cells, Schwann cells, and neurons.

and behavior.[50–55] In an analogous manner, neurons can induce T cell motility in the PNS. Aging sciatic nerve neurons express elevated levels of the chemokine CXCL13, which acts as a chemoattractant for T cells to promote age-dependent neurodegeneration in response to injury.[56]

Generally, neurons communicate with their cellular neighbors by transmitting electrical activity through one of three mechanisms: (1) the establishment of gap junctions, (2) the formation of *bona fide* synapses, and (3) the release of neurotransmitters and paracrine factors.

Gap junctions are intercellular channels containing transmembrane proteins (connexins) that permit the direct transfer of ions and small molecules between cells. During cortical neurogenesis, these specialized conduits couple ventricular zone stem cells (tanycytes, radial glial cells) with embryonic neural progenitors to form functional circuits that exhibit synchronous depolarization.[57,58] In this manner, tanycytes directly communicate with one another through connexin-43-containing gap junctions to create an electrical syncytium. Similarly, radial glial cells can use gap junctions for the propagation of calcium currents to control cortical neuron production. Gap junctions can also create neuronal circuits with postnatal neural progenitors,[59] as well as with mature astrocytes, to mediate synaptic plasticity and learning.[60,61]

In addition to gap junctions, neurons can form *bona fide* synapses on OPCs,[62] where a presynaptic neuron creates a synapse with a post-synaptic structure on an OPC to allow for signal transduction. Similar to canonical neuron-to-neuron synapses, these intercellular junctions facilitate the rapid transfer of information via presynaptic neurotransmitter release and post-synaptic neurotransmitter receptor-mediated signal transduction.[63] Although the exact mechanism governing the generation of neuron-OPC synapses remains to be fully elucidated, experience (e.g., learning, light exposure) and neuronal activity stimulate OPC proliferation and differentiation, which, in turn, regulate adaptive myelination and motor function.[30,64–67]

Synaptic transmission between two neurons typically involves neurotransmitter release from a presynaptic neuron, resulting in neurotransmitter receptor activation and downstream signaling within a post-synaptic neuron. These chemical synapses are classified according to the specific neurotransmitter released and can result in either inhibitory (e.g., GABA-mediated) or excitatory (e.g., glutamate-mediated) effects on post-synaptic neuron function.

In addition to traditional inter-neuronal inhibition or excitation, neurotransmitter secretion by neurons can also regulate neural progenitor cell proliferation, migration, and differentiation, independent of the formation of *bona fide* synapses.[40,68] For example, non-synaptic glutamate and GABA release causes ventricular zone neural stem cell depolarization through ionotropic glutamate and GABA receptors expressed on neural progenitor cells[69] to increase their proliferation during forebrain development.[70,71] Other neurotransmitters can similarly regulate postnatal neurogenesis.[72–76] For example, depletion of dopamine, which is present during early neuronal development and in adult subventricular zones, or loss of dopamine (D2 and D4) receptor function, results in reduced proliferation of neural progenitor cells.[75,76] Similarly, acetylcholine reduction decreases neurogenesis in the hippocampus, whereas increased acetylcholine-mediated muscarinic receptor signaling increases neural stem cell proliferation.[77]

Besides neurotransmitter secretion, neurons can establish other paracrine relationships with non-neuronal lineage cells. Release of neurotrophins, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), is regulated by neuronal activity,[78,79] and has profound effects on the proliferation, migration, maturation, survival, and myelination capacity of oligodendrocytes and their precursors.[80–82] For example, neuronal activity can influence microglia and T cell biology. In this manner, neuronal activity-dependent secretion of chemokines, such as Cx3cl1,[83] or neurotransmitters, such as glutamate, dopamine, and GABA,[84–86] attracts microglia to

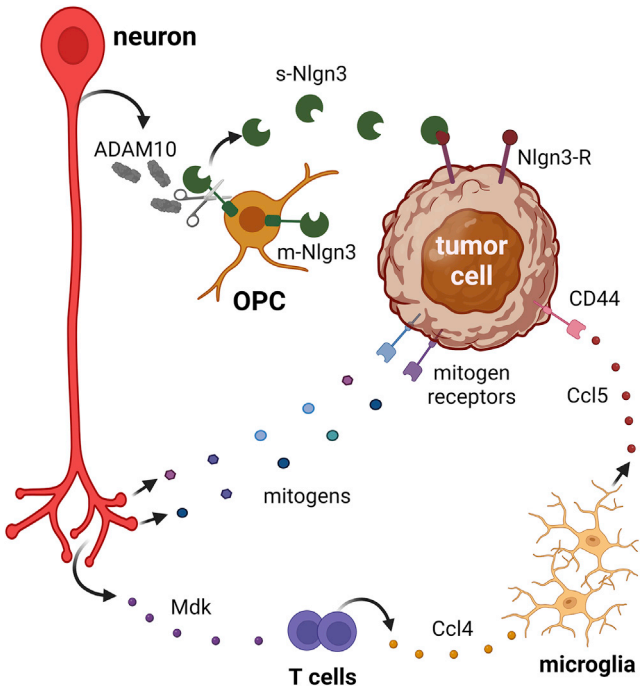

Figure 2. Neurons interact with tumor cells through the elaboration of paracrine factors

Neurons can increase tumor cell growth through activity-regulated cleavage (ADAM10-mediated) of membrane-bound Nlgn3 (m-Nlgn3) to generate a bioavailable soluble Nlgn3 molecule (s-Nlgn3) that increases tumor cell growth. Neurons also control tumor cell growth either directly through secretion of other mitogens that bind mitogen receptors on tumor cells, or indirectly through immune cells (T cells and microglia) via the elaboration of paracrine factors (midkine [Mdk]; Ccl4; Ccl5).

modulate their activation and phagocytic function. In addition, T lymphocytes located in the meningeal spaces and choroid plexus produce inflammatory mediators (IL-4, IFN-γ) that regulate neuronal function and excitability relevant to normal mouse learning and behavior.[51,53,87]

NEURONAL REGULATION OF NERVOUS SYSTEM TUMOR FORMATION AND GROWTH

Taking advantage of already established interactions important for healthy nervous system development and maintenance, neurons also regulate the formation and growth of CNS and PNS tumors. Neuronal activity governs tumor formation and progression through multiple mechanisms, including (1) the establishment of paracrine factor dependencies involving growth factors, cytokines and neurotrophins (Figure 2), (2) non-synaptic neuron–tumor cell electrical coupling via microtubes (Figure 3), and (3) the formation of *bona fide* glutamatergic synapses (Figure 3). In addition, neuronal control of cancer cell growth can be strengthened through the aberrant expression of ion channels by the cancer cells themselves.

Neuron–tumor cell paracrine relationships regulate tumor initiation

Neuronal activity can directly drive the development (initiation) of both low- and high-grade CNS tumors (gliomas). Murine models of the neurofibromatosis type 1 (NF1) cancer predisposition syndrome[88] that form low-grade gliomas of the optic nerve and chiasm (optic pathway gliomas; OPGs) were employed to define the role of neuronal activity in tumorigenesis. Since the axons of the optic nerve originate in the retina (retinal ganglion cells [RGCs]) and transmit light-induced photoreceptor signals to the brain, optogenetic stimulation of optic nerve activity increases optic glioma cell proliferation, whereas light deprivation (dark rearing) prevents tumor formation.[89] The molecular etiology for this activity-dependent regulation of gliomagenesis reflects the impact of *Nf1* mutation on RGC neuronal activity. *Nf1* mutation in RGCs causes increased production of a proteolytic enzyme, A Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10), as a consequence of increased neuronal activity. ADAM10 then cleaves a membrane-bound protein, neuroligin-3 (Nlgn3), expressed on OPCs[90] to generate a soluble bioactive protein capable of increasing tumor cell proliferation. Consistent with their roles in tumor initiation, both genetic *Nlgn3* loss and pharmacologic ADAM10 inhibition abrogate *Nf1*-OPG formation.

Analogously, using an autochthonous murine model of adult malignant glioma originating from oligodendroglial progenitors, odorant stimulation and subsequent olfactory receptor neuronal activation results in the preferential development of tumors within the olfactory bulb, where the majority of olfactory signals are processed.[91] In this model, high-grade glioma formation results from activity-dependent olfactory receptor neuron insulin growth factor-1 production, which, in turn, induces the principal olfactory output neurons (mitral and tufted cells) to drive gliomagenesis.

Neuron–tumor cell paracrine relationships regulate tumor progression

In addition to their capacity to stimulate tumor development (initiation), neuron activity-dependent paracrine factors also regulate tumor progression (continued growth after tumor induction). Using a xenograft model of high-grade glioma, optogenetic induction of neuronal activity increases tumor growth through the elaboration of NLGN3 from OPCs,[92] which results from the cleavage of NLGN3 by neuron-produced ADAM10. Similar to *Nf1* low-grade optic gliomas, ADAM10 inhibitors reduce high grade-glioma growth *in vivo*,[90] serving as the preclinical foundation for a recent clinical trial (NCT04295759). In addition to NLGN3, neurotrophins (e.g., BDNF and NT3) have been shown to increase the growth of both low-grade and high-grade glioma cells through the engagement of their cognate receptors expressed on cancer cells.[78,89,92,93] Further supporting a role for growth factor signaling in glioma biology, pediatric low-grade gliomas (pilocytic astrocytomas) can arise from mutations in the BDNF receptor (NTRK2) or fibroblast growth factor receptor 1 (FGFR1).[71,94] In a similar fashion, progression of oral mucosa carcinomas in nutrient-poor microenvironments depends upon tumor-associated nociceptive neuron secretion of NGF-triggered calcitonin gene-related peptide (CGRP).[95]

Neurons also create supportive microenvironments for brain tumor progression through communication with immune system cells. In this regard, neurons produce many cytokines and chemokines that attract and control T cell and monocyte function.[96] As such, following rabies infection, neurons produce CXCL10,[97]

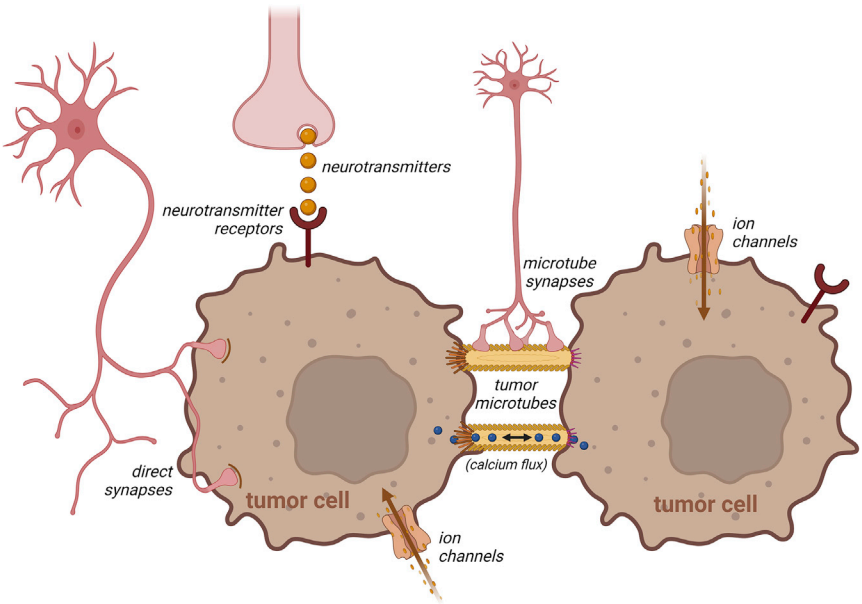

Figure 3. Neurons directly and indirectly interact with tumor cells

Neurons form *bona fide* synapses or respond to local neurotransmitters to regulate tumor cell growth, which are propagated between adjacent tumor cells through tumor microtubes, thus creating interconnected electrically coupled syncytia. Aberrant expression of ion channels on cancer cells can additionally modulate tumor expansion, and neurons can also directly synapse onto tumor microtubes.

whereas bacterial infection induces neuronal cytokine and chemokine production[98] to recruit T lymphocytes. Additionally, neurons are the major source of CX3CL1 (fractalkine), a potent chemoattractant for resident brain microglia.[99] In the setting of pancreatic cancer, increased vagus nerve cholinergic signaling reprograms the immune microenvironment, resulting in decreased $CD8^+$ T cell infiltration, altered T helper cell ratios, and increased tumor growth.[100] Conversely, severing the vagus nerve (vagotomy) reverses these effects on T cells and improves mouse survival. Additionally, in *Nf1*-optic glioma mice, where low-grade glioma progression is dependent upon T cell and microglia interaction,[101] interrupting immune cell function during tumor evolution inhibits optic glioma progression.[102] In these tumors, *Nf1*-mutant RGCs (neurons) secrete midkine, which stimulates T cells to produce Ccl4.[103,104] Ccl4 then induces the elaboration of Ccl5 from microglia to increase tumor cell growth.[104]

Finally, comparing *Nf1*-mutant mouse strains with different propensities to develop CNS (optic gliomas) and PNS (neurofibromas) tumors, neurons from mice with tumor-causing *Nf1* gene mutations are inherently hyperexcitable.[105] This basal hyperexcitability is mediated, in part, by the hyperpolarization-activated cyclic nucleotide gated potassium channel (HCN), such that agonism (lamotrigine) or antagonism (ZD7288) of HCN channel function modulates neuronal mitogen elaboration in both CNS and PNS neurons. In the setting of *Nf1*-optic gliomas, reduced HCN channel function increases midkine production in RGCs relevant to optic glioma growth. Analogously, in the PNS, sensory neurons that are in close association with peripheral nerve sheath tumors (neurofibromas) make collagen (Col1a2) in an activity-dependent manner.[105] Conversely, mice with a germline *Nf1* mutation found in NF1 patients who do not develop either gliomas or neurofibromas lack neuronal hyperexcitability and do not form brain or peripheral nerve tumors, owing to a failure to induce increased neuronal midkine and Col1a2 expression, respectfully. Important for future potential therapeutics, treatment of *Nf1*-mutant mice harboring optic gliomas or neurofibromas with lamotrigine to restore HCN channel function and dampen neuronal hyperactivity attenuates tumor progression *in vivo*.

With respect to *Nf1*-optic glioma formation and progression, the finding that tumor initiation is controlled by visual experience (light-induced RGC activity), whereas basal neuronal hyperexcitability regulates tumor progression through midkine-mediated immune microenvironment support, suggests that neurons have the capacity to control different phases of tumorigenesis in an activity-dependent manner. The fact that visual experience controls the ADAM10/NLGN3 axis, but not midkine production, and HCN1 modulation only affects midkine expression, raises the intriguing idea that neuronal excitability can be fine-tuned to alter the tumor microenvironment throughout the life cycle of cancer, as well as potentially in response to treatment.

Non-synaptic potassium-evoked currents amplified in a gap-junction-coupled network

Non-synaptic potassium currents originating from neurons firing in the vicinity of cancer cells can develop as a consequence of neuronal potassium leaking into the extracellular space. Inward rectifying channels expressed on cancer cells then uptake this leaked potassium, causing calcium influx into the glioma cells, which can be propagated through a network of glioma cells via gap junctions (Figure 3). These specialized gap junctions, named tumor microtubes, also known as tunneling nanotubes or cytonemes, facilitate long-range communication between cells and allow for the transfer of mitochondria, proteins, and infectious particles.[106–109] Tumor microtubes are similar to membrane tubes formed by healthy tissues,[110] resembling long cellular protrusions.[106] Tumor microtubes comprise thicker tubes that arborize into thinner ones, mitochondria (indicative of local ATP production and vesicle trafficking), and actin filaments—all features reminiscent of axonal and dendritic outgrowths.[28,106] Moreover, glioma microtubes contain connexin-43, a gap junction protein involved in regulating the synchronicity of calcium current propagation and the propagation of spontaneous excitatory post-synaptic currents.[106]

In gliomas, microtubes also act as post-synaptic contacts for neurons, enabling rapid coupling between nerves and neuron-stimulated glioma cells. These junctions transmit calcium waves to other glioma cells to form a functional network.[106] This syncytial electrical coupling not only increases the growth of glioma

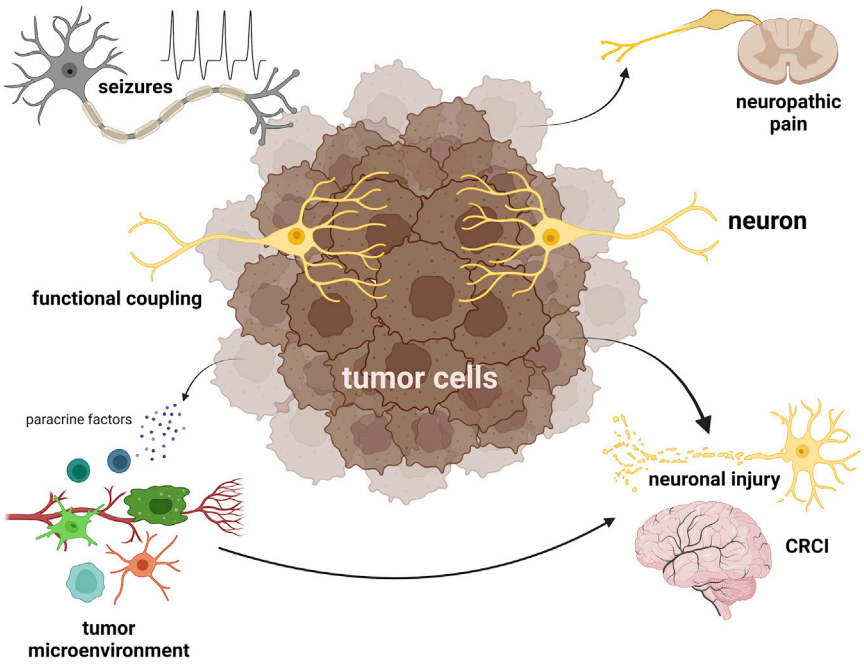

Figure 4. Tumors interact with non-neoplastic cells in the tumor microenvironment to influence their local milieu and create neuronal dysfunction

Gliomas are functionally coupled with neurons in the brain to impair normal brain function, induce seizures, or cause pain. Additionally, nervous system tumors secrete paracrine factors that modify the tumor microenvironment to increase tumor growth or promote resistance to anti-neoplastic therapies, but also interrupt the normal relationships between glial cells and neurons relative to chemotherapy-related cognitive impairment (CRCI) and neuronal injury.

cells, but also regulates their motility and invasiveness.[111] As such, tumors connected by a network of tumor microtubes are largely protected from the cytotoxic effects of radiation[106] and chemotherapy,[112,113] whereas unconnected tumor cells are susceptible to treatment:[114] genetic silencing of the connexin-43 gap junction protein found in tumor microtubes decreases the radioprotective effect of the tumor microtube network. Clinically, the presence of microtubes is related to tumor aggressiveness, as glioblastomas and astrocytomas form expansive tumor microtube networks, whereas oligodendrogliomas, which are less invasive, do not form such junctions.[106]

Bona fide neuron-glioma synapses

Electron microscopy revealed the presence of *bona fide* neuronal synapses on human high-grade glioma cells xenografted into mice[115,116] (Figure 3). These synapses are also seen in experimental mouse models of low-grade optic pathway glioma,[89] as well as in murine glioblastoma, fresh operative human glioma specimens *in situ*, human glioma cells co-cultured with neurons *in vitro*[116] and patient-derived xenograft models.[111] Similar to neuron-neuron synapses, neuron-glioma synapses exhibit the hallmark features of glutamatergic synapses and contain presynaptic vesicles, a synaptic cleft, a presynaptic active zone with docked vesicles, and a post-synaptic density area.[116] Further characterization of these neuron-glioma synapses has revealed three main morphological types: (1) single synaptic contacts onto glioma microtubes, (2) multi-synaptic contacts with both glioma microtubes and other neurons, and (3) ''pseudo-tripartite'' perisynaptic connections.

Bona fide glutamatergic synapses are formed between neurons and glioma cells through ionotropic glutamate (AMPA) receptors to induce glioma cell membrane depolarization and calcium influx. These synapses primarily form on tumor microtubes, whereas some exist on glioma cell bodies (somas).[116] As only a small proportion of the tumor cells are connected to neurons, these synapses generate calcium currents and stimulate the entire glioma network through the induction of new tumor microtubes between cancer cells[111] or existing tumor microtube networks.[106] This enhanced neuronal activity and glutamatergic signaling facilitates tumor invasion[111,117,118] and proliferation.[119] Importantly, regardless of the underlying mechanism, membrane depolarization itself can drive glioma cell growth.[115] Conversely, genetic silencing of the AMPA GluR1 subunit on tumor cells inhibits glioma proliferation,[120] whereas AMPA receptor blockade suppresses cancer cell migration and induces apoptosis[121] through the Akt signaling pathway.[122]

In addition to glutamate, other neurotransmitters, including acetylcholine[123] and dopamine,[75] have been implicated in brain cancer progression, reminiscent of their pro-tumorigenic role in peripheral solid tumors.[124,125] Using a high-content neurochemical compound screen, antagonists to dopamine receptor D4 (DRD4) signaling, as well as to serotonergic and cholinergic neurotransmission, were found to selectively inhibit malignant glioma cell growth and increase the differentiation of non-neoplastic neural stem cells. As such, blockade of DRD4 on cancer cells results in an accumulation of autophagic vacuoles, cell cycle arrest, and apoptosis. Inhibition of tumor progression by targeting dopamine G protein-coupled receptors (GPCRs) nicely parallels the observation that pharmacologic interruption of GPCR-cyclic AMP signaling attenuates malignant brain tumor growth.[74]

In contrast to the *bona fide* synapses in primary gliomas, metastatic tumors to the brain, such as breast-to-brain metastases, associate with neurons in a perisynaptic manner without establishing true synaptic connections.[126] In these tumors, excitatory (glutamatergic) neurons transmit glutamate through pseudo-tripartite synapses, akin to those formed by neurons and astrocytes in the normal brain.[127] These pseudo-tripartite synapses increase glutamatergic signaling through NMDA receptors on the tumor cells and promote metastatic cancer colonization and spread. However, the biological function of pseudo-tripartite synaptic structures in the setting of primary gliomas is not clear. Similarly, whether actual synapses are

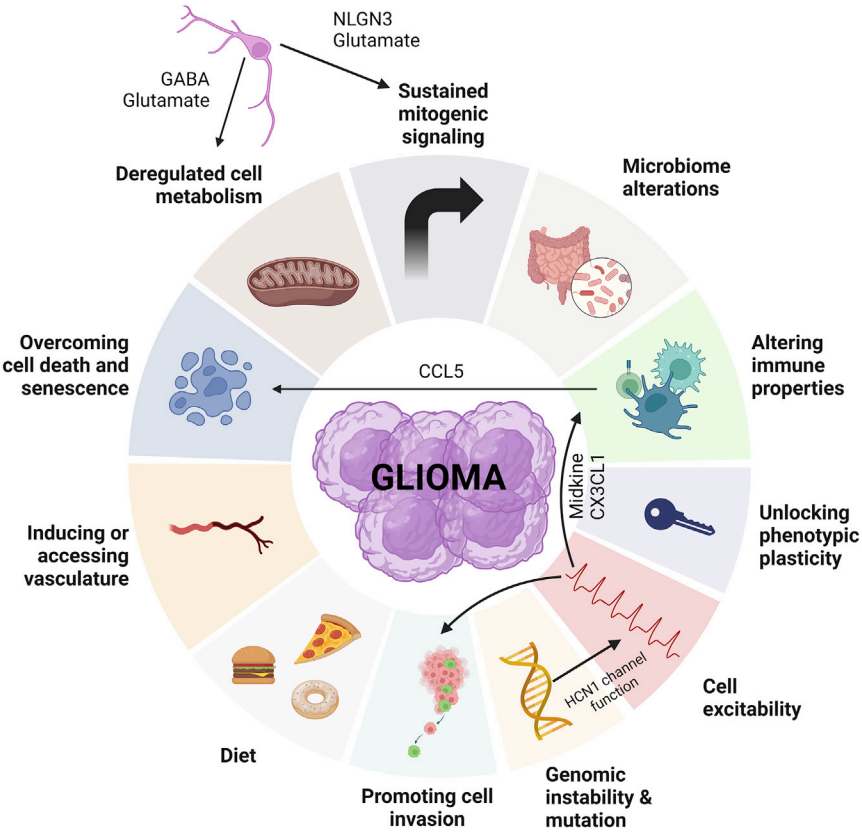

Figure 5. Integrated hallmarks of cancer
Modification of the hallmarks of cancer, now incorporating the relationships between cell (neuron and tumor cell) excitability and other properties, such as genetic mutation, cell invasion, cell metabolism, immune properties, mitogenic signaling, and cell death/senescence, as relevant to brain tumor (glioma) pathobiology. Some of these hallmarks have the capacity to functionally influence each other. For example, tumor-associated *NF1* mutations in neurons cause hyperexcitability and the elaboration of midkine to induce T cell-microglia (immune) support of *Nf1*-optic glioma cell survival through CCL5.

formed between peripheral neurons and PNS tumors remains to be fully elucidated.

Cancer cell ion channels

Often overexpressed in cancer cells, ion channels convert neuron-derived extracellular cues into intracellular molecular cascades[128,129] that coordinate cell excitability with cell proliferation[130] and migration.[131] Specifically, these ion channels include anion (chloride-conducting) and cation (potassium-, sodium-, and calcium-conducting) channels,[132–134] as well as non-selective transient receptor potential (TRP) channels.[135,136] The presence of such cation (calcium) microtubes permits cancer cell network connectivity and autonomous rhythmic activity within a subset of glioblastoma cells, which collectively acts to increase overall tumor growth.[137] Although some of the etiologic mechanisms remain incompletely characterized, the CLIC1 chloride channel, overexpressed by many cancers, regulates brain tumor cell cycle progression.[138] Similarly, increased potassium channel expression in brain tumors[139,140] supports cancer stem cell viability,[141] whereas the PIEZO mechanosensitive cation ion channel, overexpressed in glioma, is associated with poor patient prognosis.[142] In addition, overexpression of the TRPV1 channel in gliomas regulates tumor cell survival through endoplasmic reticulum stress pathway activation,[143] whereas overexpressed TRPM7 channel controls glioma cell migration, invasion, and proliferation.[144] These findings prompted the report of an 18-ion channel gene signature, which was found to be predictive of overall survival in patients with glioma.[145]

COMPLICATIONS OF CANCER

Tumors of the nervous system not only depend upon neurons for regulation of cancer formation and progression, but also their intimate relationship with neurons also influences normal nerve cell function, both at baseline and in the setting of tumor treatment. These effects include tumor-induced neuronal hyperexcitability and chemotherapy-induced neuronal dysfunction (Figure 4).

Since brain tumors arise within an existing functional network critical for normal brain function, it is not surprising that they can become integrated into these same circuits. As such, gliomas locally disrupt the synchronization of neural communication, which is important for processing motor and sensory information. Additionally, the infiltration of tumor cells with the ability to engage in electric or chemical synapse transmission could create new integrated circuits or degrade the amount and quality of information transmitted in these functional networks. Using intraoperative electrocorticography and magnetoencephalography in subjects with malignant glioma, tumor-infiltrated cortex was found to engage in coordinated neural responses, which impaired normal language processing.[146,147] Similarly, motor and language function is inhibited by electrical stimulation of glioma-infiltrated cortex,[148] and resection of tumor-infiltrated brain regions with high degrees of functional connectivity causes permanent neurological damage.[147]

Although electrochemical neuron-glioma communication is traditionally thought to occur between presynaptic neurons and post-synaptic glioma cells, this interaction is in fact bidirectional. The tight integration of glioma cells into functional neuronal networks also affects normal neuronal activity through the induction of hyperexcitable states (seizures). In this regard, seizures occur in 40%–80% of individuals with glioma.[149–151] Increased neuronal excitability and seizures could result from the release of glutamate from glioma cells or a reduction in GABAergic inhibition:[152–154] inhibition of glutamate release from tumor cells reduces the frequency of seizures in glioma-bearing mice.[153] Additionally, glioma cells can transfer genetic material to neighboring neurons via extracellular vesicles, which increases neuronal activity and ultimately stimulates tumor growth.[155] To

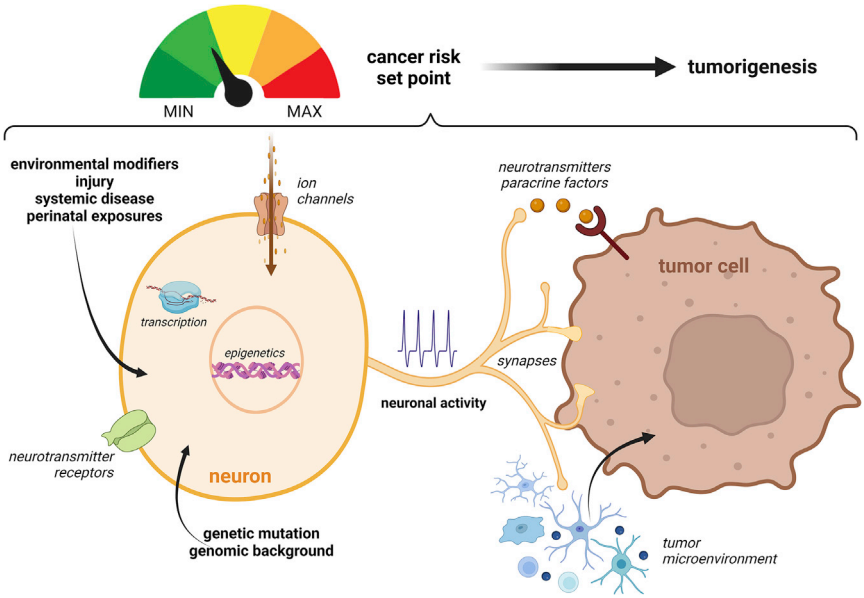

Figure 6. Risk factors operate at the level of the neuron to modulate cancer risk

Operating at the transcriptional or epigenetic level, genetic mutations and genomic background can alter neuronal excitability in numerous ways, including ion channel and neurotransmitter receptor function, the formation of neuron–tumor synapses, and the elaboration of paracrine factors that act either directly on cancer cells or indirectly through non-neoplastic cells in the tumor microenvironment. Environmental factors, nervous system injury, systemic diseases, and perinatal exposures (infection) can additionally operate to disrupt interactions between neurons and cancer cells, such that the combination of these factors establish a ground state of neuronal excitability that makes cancer development more or less likely to occur.

gain insights into other possible mechanisms for the reciprocal crosstalk between neurons and glioma cells, an *in vivo* high-throughput screening study revealed that some *PIK3CA* gene mutations selectively initiate neuronal excitability through differential glioma cell secretion of glypican-3 (GPC3).[156] These GPC3-driven tumors have greater excitatory and inhibitory synapse formation, resulting in seizure induction and further enhancement of glioma growth. Conversely, genetic silencing of *GPC3* in glioma cells eliminates the early onset neuronal hyperexcitability and extends mouse survival.

The intimate relationship established between neurons and oligodendrocytes is important for adaptive myelination in the healthy brain[29,30] and can be disrupted following anti-cancer treatment. One of the unintended consequences of chemotherapy is the development of chemotherapy-related cognitive impairment (CRCI; "chemobrain"),[157] which results from impaired neuron activity-dependent myelination.[66] In a mouse model of methotrexate (MTX) chemotherapy,[158] MTX reduced neuronal BDNF expression and impaired neurotrophic receptor tyrosine kinase 2 (NTRK2) signaling in OPCs to disrupt activity-dependent myelination. This neurotoxicity involved microglia, which have also been implicated in other chemotherapy-induced cognitive impairments.[66,159,160]

Last, chemotherapy-induced peripheral neuronal damage (neuropathy) is similarly influenced by microglia,[161,162] T cells,[161,163,164] and inflammatory cytokine release.[165,166] In the setting of cancer, perineural invasion and neuropathic pain involves dysregulated neurotrophin (NGF) signaling[167,168] and/or dysfunctional neuroimmune interactions.[169,170]

IMPLICATIONS AND FUTURE DIRECTIONS

Since neurons and tumors establish bidirectional dependencies that reflect the normal connections between neurons and their local cellular milieu, it is likely that tumors create their own microenvironment by usurping existing developmental and homeostatic relationships.[12,33,171,172] Defining the molecular bases for each of these interactions will be important as we consider future therapies that interrupt neuron-cancer communication. These interventions could include repurposing drugs that inhibit neuronal hyperexcitability,[105,173] targeting tumor-specific synapses/receptors,[174] and/or employing ADAM10 inhibitors to interrupt paracrine circuits.[89,90]

In addition, the wealth of evidence arguing that neurons are key drivers of tumor formation and growth supports a reconceptualization of the hallmarks of cancer.[175] Incorporating studies from numerous laboratories in the cancer neuroscience field,[176] we now suggest including cell (neuron and tumor cell) excitability, as well as the relationships between cell excitability and other key tumor features (e.g., tumor invasion, immune cell function) as major hallmarks, using brain tumors (gliomas) as an illustrative example (Figure 5).

Moreover, the idea that neurons are central regulators of tumorigenesis[89,105] raises the provocative concept that neurons might create set points for tumor risk (Figure 6). As such, it is possible that specific cancer-associated genetic alterations (perhaps even single nucleotide variations) alter neuronal hyperexcitability through the modulation of ion channel or neurotransmitter function at the genomic or transcriptional level. For instance, postnatal loss of one of the genes implicated in the tuberous sclerosis cancer predisposition syndrome (*Tsc1*) increases the excitability of striatonigral neurons[177] due to a reduction in inhibitory transmission,[178] as well as reduces the intrinsic excitability of dopaminergic neurons.[179] Likewise, *p53* mutation, as seen in patients with Li-Fraumeni syndrome, reduces the firing frequency and the number of excitatory synapses formed in layer 5 pyramidal neurons of the mouse primary somatosensory cortex.[180] As described above, different NF1 patient germline *NF1* mutations have varying effects on neuronal hyperexcitability, which, in turn, differentially dictate tumor formation and progression in mice.[105] In addition to the specific gene mutation, environmental factors, tissue injury, systemic diseases, and perinatal infections likely also modify cancer risk by interrupting the interactions between neurons and other cell types. In this regard, we have found that asthma, which is associated with reduced risk of glioma in children with NF1, modifies

neuroimmune interactions[102] critical for establishing a microenvironment supportive of brain tumor growth.[103] Further work on these and related risk factors may identify new intersections between neurons and tumor cells relevant to future precision medicine strategies.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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