



Published in final edited form as:

Nature. 2023 June ; 618(7965): 467–479. doi:10.1038/s41586-023-05968-y.

The neuroscience of cancer

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Abstract

The nervous system regulates tissue stem and precursor populations throughout life. Parallel to roles in development, the nervous system is emerging as a critical regulator of cancer, from oncogenesis to malignant growth and metastatic spread. Various preclinical models in a range of malignancies have demonstrated that nervous system activity can control cancer initiation and powerfully influence cancer progression and metastasis. Just as the nervous system can regulate cancer progression, cancer also remodels and hijacks nervous system structure and function. Interactions between the nervous system and cancer occur both in the local tumour microenvironment and systemically. Neurons and glial cells communicate directly with malignant cells in the tumour microenvironment through paracrine factors and, in some cases, through neuron-to-cancer cell synapses. Additionally, indirect interactions occur at a distance through circulating signals and through influences on immune cell trafficking and function. Such cross-talk among the nervous system, immune system and cancer—both systemically and in the local tumour microenvironment—regulates pro-tumour inflammation and anti-cancer immunity. Elucidating the neuroscience of cancer, which calls for interdisciplinary collaboration among the fields of neuroscience, developmental biology, immunology and cancer biology, may advance effective therapies for many of the most difficult to treat malignancies.

The nervous system is emerging as an important regulator of both healthy and malignant cellular niches throughout the body. Governing organ development, tissue homeostasis and regeneration throughout life, the nervous system is central to the physiological function of all organ systems, including the immune system. It is therefore not surprising that the nervous system has a similarly crucial role in a broad range of cancers. Comprising diverse neuronal and glial populations, the nervous system branches extensively throughout the body, typically travelling together with the microvasculature, to reach all tissue microenvironments except keratinized structures. This expansive network of

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Author contributions R.M. and M.M. wrote and edited the manuscript. R.M. and M.M. designed the figures. M.M. supervised all aspects of the work.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-023-05968-y>.

Competing interests M.M. holds equity in MapLight Therapeutics.

nerves similarly reaches tumour microenvironments and can contribute in critical ways to cancer pathogenesis, from tumour initiation to progression and metastasis. In turn, the nervous system is often remodelled by the cancer it regulates. In this Review, we consider interactions with the nervous system in both central nervous system (CNS) cancers and cancers outside the CNS. This emerging field of ‘cancer neuroscience’ encompasses local and systemic interactions between cancer cells and the fundamental components of the nervous system—neurons, astrocytes, oligodendrocytes, microglia, Schwann cells and peripheral nerves—and the effects of these interactions on cancer initiation, progression, the tumour immune microenvironment and metastasis. At this intersection between neurobiology and cancer biology, new neuroscience-based targets for cancer therapy are now emerging.

CNS: activity-regulated development and cellular plasticity

The role of neural activity in organ development and plasticity is best studied in the nervous system itself, and for this reason we focus the beginning of this Review on activity-regulated neurodevelopment. Nervous system development is influenced by electrical activity from the earliest stages of neurodevelopment. Ongoing refinement and plasticity of neural circuits—from synaptic plasticity to plasticity of myelin structure—is further modulated by the activity of the circuit. Cancers in the brain ultimately hijack these activity-regulated mechanisms, and many important lessons can be gleaned about cancer through a deep understanding of activity-regulated neural development and the ongoing adaptive plasticity of neural circuit form and function.

Nervous system development

Nervous system development involves the generation of neurons and glial cells from neural stem and progenitor cells, diversification and maturation of neural cells, migration to the appropriate anatomical position, assembly of functional circuits between neurons—a process that involves axon pathfinding, synapse formation, circuit refinement and establishment of the myelinated infrastructure that supports fast communication in the nervous system. Astrocytes have critical roles in the establishment of synapses during development^{1–4} and subsequently in support of synaptic function throughout life⁴. Electrical activity influences all stages of nervous system development, from neural induction during embryogenesis^{5–7} to adaptive plasticity of complex neural circuits in the adult brain (for a review, please see ref. 8). Canonical neuronal activity—involving neurotransmitter release at mature electrochemical synapses and consequent membrane depolarization—results in voltage-dependent calcium influx that can affect a range of cellular functions^{9–11}.

At the earliest developmental stages, patterned waves of electrical activity trigger calcium transients in developing neural tissues that are critical for both cellular and synaptic patterning. In the embryonic cerebrum, neural stem cells are coupled by gap junctions to one another and membrane depolarization-induced calcium transients propagate synchronously through the germinal zone to regulate stem cell proliferation^{12,13}. Neurotransmitters—secreted by a variety of cell types in a non-synaptic manner during developmental stages that precede synapse formation—generally promote neurogenesis^{14–17}. The migration of

developing neurons is influenced by voltage-dependent mechanisms, including through transient synapses from subplate neurons onto migrating neocortical neuroblasts¹⁸, and neuronal activity also instructs pathfinding and targeting of axons from nascent neurons^{19–21}.

The gap junctional coupling that occurs between stem and progenitor cells also takes place among various populations of neuroblasts and neurons during later stages of neurodevelopment^{22–26}. This coupling, together with mechanisms such as extrasynaptic glutamate and ‘pacemaker’ neurons that oscillate spontaneously (see ref. 27 for a review), enables synchronized, action potential-dependent calcium transients to spread through the developing nervous system^{26,28–34}. Such experience-independent, coordinated waves of activity are thought to promote the assembly of functional neural circuits through the Hebbian principle³⁵, and these circuits are later refined in an experience-dependent manner (for a review, see refs. 36,37).

Postnatal neurodevelopment and ongoing neuroplasticity

In the postnatal brain, neuronal activity and neurotransmitter-mediated mechanisms continue to govern new cell generation from neural stem and precursor cells in neurogenic niches^{38–43}. As in neuron generation, the generation of myelinating oligodendrocytes is regulated by neuronal activity throughout life. Myelination of the CNS—the process by which oligodendrocytes ensheath axons to facilitate fast saltatory neural conduction⁴⁴ and to provide metabolic support to axons⁴⁵—requires the proliferation and differentiation of oligodendrocyte precursor cells (OPCs), which are distributed throughout the nervous system across the lifespan⁴⁶. Myelin development extends over a protracted postnatal period spanning at least three decades in humans^{47–49} and continues throughout life in certain regions such as the neocortex^{48,50–54}. Extrinsic cues driven by neuronal activity and experience modulate developmental myelination and drive ongoing myelin plasticity (for a review, please see ref. 55). Neuronal activity can elicit proliferation of oligodendroglial precursor cells that generate new oligodendrocytes and alter myelination in an activity-regulated manner^{51,56–59}. Such adaptive plasticity of myelin tunes neural circuit function^{59,60} and contributes to cognition^{57,59,61,62}.

Activity-regulated communication between neurons and OPCs involves paracrine mechanisms such as secretion of neurotrophic factors. In addition to its numerous roles in neurodevelopment and plasticity, brain-derived neurotrophic factor (BDNF) promotes both developmental myelination^{63,64} and ongoing myelin plasticity⁵⁷. Also mediating neuron–glial communication are bona fide glutamatergic and GABAergic neuron-to-OPC synapses^{65–68}. While much remains to be learned about the function of these well-characterized but still somewhat enigmatic neuron-to-glial synapses, present evidence indicates that AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor-dependent synapses on OPCs regulate cell survival⁶⁹.

Neuronal activity drives glioma initiation and progression

It is on this backdrop of neuronal activity-regulated brain development and plasticity that we must consider the interactions of neurons with brain cancers. The most common

primary brain cancers in both children and adults are gliomas, which contain heterogeneous tumour cells including subpopulations of oligodendroglial-like and astrocyte-like cells^{70–72}. Although these cancers were originally named ‘astrocytomas’ because of histological characteristics reminiscent of astrocytes, it is now understood that most forms of glioma arise from stem and precursor cells in the oligodendrocyte lineage^{71–80}. The robust mitogenic effect of neuronal activity on OPCs discussed above suggests that dysregulated or ‘hijacked’ mechanisms of myelin plasticity might similarly promote malignant cell proliferation in this devastating group of primary brain cancers. Indeed, neuronal activity promotes proliferation and growth of both high-grade^{81,82} and low-grade⁸³ glioma subtypes in preclinical models (Fig. 1). Optogenetic stimulation of cortical projection neurons drives the growth of patient-derived high-grade glioma xenografts within the stimulated circuit⁸¹. Similarly, optogenetic stimulation of retinal ganglion cell axons in the optic nerve increases low-grade glioma growth in a genetically engineered mouse model of neurofibromatosis 1 (NF1)-associated optic pathway glioma⁸³. Conversely, chemogenetic suppression of olfactory neuronal activity, or reduced olfactory experience through mechanical naris occlusion, decreases tumour growth in a genetically engineered mouse model of olfactory bulb high-grade glioma⁸².

Neuronal activity not only promotes growth of established glioma tumours, but also regulates glioma initiation and maintenance. In a mouse model of optic pathway glioma driven by mutations in the *Nf1* gene, visual experience-induced stimulation of optic nerve activity during a developmental period of tumour susceptibility was necessary for optic pathway glioma tumour formation and maintenance. Despite the genetic predisposition to and high penetrance of optic pathway gliomas in this model, tumours did not form when optic pathway activity was reduced by dark-rearing the mice just before the time tumours typically form, in stark contrast to universal tumour formation in littermate control animals raised with normal visual experience⁸³. Decreasing visual experience just after the time that tumours typically form also blocked optic pathway tumour maintenance⁸³. Similarly, in a mouse model of *IDH*-wild-type high-grade glioma that preferentially forms in the olfactory bulb, modulating olfactory experience and olfactory neuronal activity through unilateral naris occlusion regulates tumour formation ipsilateral to the occluded naris⁸². These two studies underscore an emerging principle that sensory experience can modulate cancer progression in cancers located within that sensory circuit (Fig. 2), further discussed below with respect to immune modulation and for cancers of the skin and pancreas.

Paracrine mechanisms of neuronal activity-regulated glioma progression

Paracrine signalling mechanisms are one crucial way that neuronal activity regulates glioma growth (Fig. 1). Activity-regulated paracrine secretion of both BDNF and the synaptic protein neuroligin-3 (NLGN3) promotes the proliferation of high-grade^{81,84} and low-grade⁸³ gliomas. In the genetically engineered mouse model of olfactory bulb high-grade glioma discussed above, insulin-like growth factor-1 (IGF-1) was identified as the key neuronal activity-regulated paracrine factor driving olfactory bulb glioma growth, suggesting region- or circuit-specific mechanisms of neuron–glioma interactions⁸². Given the many different subtypes of neurons that exist, such circuit-specific—and neuron subtype-specific—mechanisms are not surprising. Not all activity-regulated paracrine signalling mechanisms

involve direct neuron–glioma interactions. In an example of neuron–immune–cancer cell cross-talk (Fig. 3) leading to tumour growth-promoting inflammation, retinal ganglion cell neurons secrete midkine, which stimulates CD8⁺ lymphocytes to secrete the chemokine CCL4, which in turn stimulates glioma-associated microglia/macrophages to secrete CCL5 that acts on NF1-associated optic pathway low-grade glioma cells to promote tumour maintenance and progression^{85,86}. Such neuron–immune cell–glioma interactions highlight the influence of the nervous system in regulating the tumour immune microenvironment in ways that can influence both pro-tumour inflammation and anti-cancer immunity, an emerging principle probably relevant to numerous forms of cancer and to cancer immunotherapy, as discussed in more detail below.

The role for activity-regulated BDNF signalling in glioma⁸¹ parallels its role in promoting activity-regulated proliferation of healthy OPCs discussed above. More unexpectedly, the synaptic adhesion molecule NLGN3 has emerged as a critically important player in neuron–glioma interactions. Progression of high-grade and low-grade glial malignancies stalls in the absence of microenvironmental NLGN3 (refs. 83,84). Concordantly, mRNA⁸¹ and protein⁸⁷ expression levels of NLGN3 inversely correlate with survival in human patients with adult glioblastoma. Genetic knockout and pharmacological blockade of activity-regulated NLGN3 shedding—mediated by the ADAM10 sheddase with shedding chiefly coming from OPCs, probably from neuron-to-OPC synapses⁸⁴—demonstrate that NLGN3 is necessary for the growth of gliomas in a range of preclinical high-grade glioma models⁸⁴. In an NF1-associated optic pathway low-grade glioma mouse model, the NF1 mutation—present in all microenvironmental cells in the NF1 tumour predisposition syndrome—results in excessive NLGN3 shedding in the optic nerve⁸³ due to the hyperexcitability of NF1-mutant retinal ganglion cell neurons⁸⁸. Similar to the dependency of high-grade glioma xenograft growth on microenvironmental NLGN3, optic pathway gliomas did not form in an NF1-associated optic pathway glioma mouse model deficient in NLGN3 or in which NLGN3 shedding was pharmacologically blocked⁸³. On the basis of these preclinical findings, therapeutic targeting of NLGN3 for paediatric high-grade gliomas is presently in an early-phase clinical trial ([NCT04295759](#)).

This unexpected dependency of glioma progression focuses a spotlight on the mechanisms by which NLGN3 influences glioma pathophysiology. NLGN3 binding induces multiple oncogenic signalling pathways (upstream, focal adhesion kinase pathway; downstream, PI3K–mTOR, SRC and RAS pathways) in glioma cells⁸⁴. Although this NLGN3-regulated stimulation of oncogenic signalling pathways helps to explain the sufficiency of NLGN3 in promoting glioma proliferation and growth, it does not explain the unexpected dependency on this shed synaptic adhesion protein⁸⁴. Subsequent experiments revealed that NLGN3 upregulates the expression of synapse-associated genes in glioma cells⁸⁴, raising the subsequently confirmed possibility that synapses may form between neurons and glioma cells.

Synaptic integration of glioma networks into neural circuits

A combination of electron microscopy, electrophysiology and calcium imaging studies have clearly demonstrated that glutamatergic synapses form between neurons and glioma cells in both paediatric and adult high-grade gliomas^{89,90}.

Neuron-to-glioma synapses

NLGN3 in the tumour microenvironment promotes these neuron-to-glioma synapses, suggesting that regulating synaptic integration is a key role of activity-regulated NLGN3 signalling⁸⁹. Like the neuron-to-OPC synapses that form in the healthy brain, neuron-to-glioma synapses are mediated by calcium-permeable AMPA receptors^{89,90}. Whole-cell patch clamp electrophysiology of glioma cells has shown that a subset (~5–10%) of glioma cells within a given tumour exhibit glutamatergic, AMPA receptor-mediated synapses^{89,90}, and single-cell transcriptomic studies have indicated that this subpopulation of synaptically integrated glioma cells corresponds to the malignant cells that most resemble OPCs in paediatric high-grade glioma⁸⁹ and that most resemble OPCs or neuronal precursor cells (NPCs) in adult glioblastoma⁹¹. Activity-regulated secretion of BDNF from neurons increases the strength of these glutamatergic currents in glioma cells, a finding that recapitulates the adaptive plasticity operant in healthy synapses and underscores the way that neuron–glioma interactions can be reinforced through activity-regulated mechanisms⁹².

Another subpopulation of tumour cells, representing the majority of the cells in some patient-derived glioma models, instead exhibit potassium-evoked depolarizing currents in response to neuronal activity^{89,90}. As extracellular potassium levels increase with neuronal action potentials, these glioma potassium-evoked currents scale with field potential—the more neurons are active, the larger and longer these glioma currents become⁸⁹. Furthermore, glioma cells connect to each other by gap junctions⁹³ in both adult^{93,94} and paediatric^{78,89} glial malignancies. Gap junctional coupling of glioma cells serves to amplify the potassium-evoked currents and to promote synchrony of neuronal activity-evoked calcium transients propagating through this neuron-to-glioma network of cells^{89,90}. A subset of the gap junction-coupled cells also receive synaptic inputs from neurons⁹¹, and thus this malignant glioma-to-glioma network is integrated synaptically and electrically into the brain (Fig. 1).

Evolution of malignant circuitry

How this malignant circuitry develops and evolves over the course of disease remains to be fully elucidated. Astrocytes enable the establishment of healthy neural circuits during development³ through the secretion of synaptogenic factors⁴, but the role of astrocytes in the tumour microenvironment, or of astrocyte-like glioma cells, as discussed below, in the establishment of neuron-to-glioma synapses, remains to be determined. Early insights indicate that activity-regulated signals, including NLGN3 (ref. 89) and BDNF⁹², promote malignant synapse establishment and/or maintenance, predicting that neuron-to-glioma synaptic connectivity may increase over time. Concordantly, single-cell transcriptomic examination of primary and recurrent biopsy samples from adult patients with glioblastoma demonstrates an increase in synaptic gene expression by the time of tumour recurrence⁹⁵. In adult glioblastoma, neuron-to-glioma synapses facilitate glioma invasion at the invasive edge

of the tumour in a calcium signalling-dependent manner⁹¹, mirroring the role of transient synaptic inputs in migration of neocortical neuroblasts in normal brain development¹⁸ discussed above. These synaptically connected, invasive glioblastoma cells transition to gap junction-coupled, interconnected tumour cells over time⁹¹. The extent to which activity-regulated paracrine factors promote invasion remains to be determined, but such activity-regulated invasion mechanisms would help to explain the circuit-specific and sometimes expertise-specific patterns of glioma invasion and progression observed in patients.

Cancer cell membrane depolarization

The synaptic and electrical integration of glioma into neural circuits is central to tumour progression in preclinical models; blockade of glioma AMPA receptors or gap junctions impedes glioma growth^{89,90}, whereas increasing AMPA receptor signalling accelerates glioma progression⁸⁹. Given the roles for membrane voltage changes in brain development discussed above, and given that glioma cells exhibit at least two mechanisms of activity-evoked membrane depolarization, the hypothesis that membrane depolarization itself may drive glioma proliferation was tested using an in vivo optogenetic strategy, in which channelrhodopsin-2 was expressed in xenografted patient-derived glioma cells. Reminiscent of the roles that synchronized waves of membrane depolarization have in normal neurodevelopment, in vivo optogenetic depolarization of the glioma xenografts robustly increased glioma proliferation⁸⁹ through voltage-sensitive mechanisms that remain to be defined. Underscoring the importance of these depolarizing waves and consequent calcium transients, tumour cells exhibiting autonomous, oscillatory calcium transients have been identified in both paediatric⁸⁹ and adult⁹⁶ high-grade gliomas that serve as ‘hub’ cells, driving autonomous waves of depolarization and calcium transients through the gap junction-connected network of tumour cells. These tumour cells, reminiscent of ‘pacemaker’ neurons in the developing brain, achieve these autonomous, oscillatory calcium transients through expression of the calcium-activated potassium channel KCa3.1, which has a similar role in sinoatrial cardiac cells⁹⁶. These glioma cells exhibiting periodic depolarization are extensively connected to the tumour network and thus serve as a ‘hub’ of depolarizing current, with important functional consequences for glioma growth⁹⁶. Further emphasizing membrane voltage-dependent mechanisms in brain cancer, voltage-gated sodium channel expression in a *Drosophila* brain tumour model regulates tumour growth just as it does *Drosophila* neuroblast development⁹⁷. These mechanistic parallels between normal and malignant neuron–glial interactions underscore the extent to which mechanisms of neurodevelopment and plasticity are subverted by malignant gliomas and the importance of understanding the neuroscience of brain cancers. Given the many different subtypes of neurons in the CNS, much remains to be uncovered about the interactions between various neuronal types and brain cancer cells that may inform patterns of cancer growth and invasion in the CNS and elucidate important therapeutic targets.

Synaptic pathophysiology in brain metastases

Synaptic pathophysiology is not restricted to primary brain cancer. In the context of breast-to-brain metastases (B2BMs), tumour cells can co-opt neuronal programmes to promote metastatic growth in the brain. Recent immunohistochemical analysis of primary human breast cancer samples, along with brain metastasis samples, demonstrated substantial

expression of glutamatergic NMDA receptors, which are involved in excitatory synaptic transmission⁹⁸. Further electron microscopy analysis showed that these NMDA receptor-expressing B2BM cells localize at glutamatergic synapses, forming pseudo-tripartite synapses at glutamatergic terminals where glutamate released at neuron-to-neuron synapses can stimulate the perisynaptic breast cancer cell. Knockdown of these NMDA receptors in human B2BMs substantially reduced colonization and growth in the brain following intracardiac injection of human B2BM cells in an immunodeficient mouse model⁹⁸. Taken together, these results demonstrate a mechanism by which cancer cells can express neuronal machinery to enhance their metastatic growth potential in the brain.

Effects of glioma on neurons

Just as neuronal activity drives glioma initiation, growth and progression, glioma cells increase neuronal excitability and thus neuronal activity^{89,99–103}. Gliomas have long been associated with seizures, and pioneering work from the Sontheimer group demonstrated that gliomas directly increase the excitability of neurons¹⁰⁰. This occurs through numerous mechanisms that include non-synaptic secretion of glutamate from adult glioblastoma cells through the glutamate–cysteine exchanger system X_c (refs. 99,104), loss of inhibitory neurons in the tumour microenvironment^{101,104}, changes in the neuronal response to GABA (γ -aminobutyric acid)¹⁰¹ and glioma secretion of synaptogenic factors such as glypican-3 (refs. 102,103) and thrombospondin-1 (TSP-1)¹⁰⁵. Synaptogenic factor secretion is an important function of normal astrocytes, and astrocyte-like glioma cell subtypes are thought to be responsible for the synaptogenic factor secretion driving glioma-associated seizures¹⁰². Fascinatingly, different point mutations in the same oncogene (*PIK3CA*) influence the extent to which glioma cells induce hyperexcitability through differential glypican-3 secretion in adult *IDH*-wild-type glioblastoma models¹⁰³, indicating that the molecular characteristics of the glioma may account for heterogeneity in the mechanisms and robustness of neuron–glioma interactions. In an immunocompetent mouse model of adult glioblastoma, early microglial infiltration was observed before the onset of seizures and microgliosis increased as tumour-associated seizures worsened over the disease course, suggesting a possible role for tumour-associated microglia in remodelling cortical network excitability¹⁰⁴.

The hyperexcitability of the glioma-infiltrated cortex first described in mice has now been confirmed using intraoperative electrocorticography in awake, resting adults with glioblastoma⁸⁹ and those executing cognitive tasks¹⁰⁵. As a measure of oscillatory brain activity, broadband power measurements obtained using magnetic encephalography (MEG) in adults with glioma indicate an inverse relationship between global and peritumoral broadband power and progression-free survival^{87,106}. Glioma-induced neuronal hyperexcitability is thought to contribute to glioma-associated seizures^{99,100,102,103} and to augment the tumour-promoting effects of neuronal activity. These feed-forward, bidirectional neuron–cancer interactions represent a principle found in numerous types of cancer, as discussed below (Figs. 1 and 4).

Glioma-derived synaptogenic factors not only influence neuronal excitability, but also can promote functional remodelling of neural circuits¹⁰⁵. Intraoperative electrophysiological studies have shown that adults with *IDH*-wild-type glioblastoma involving the language-

associated cortical areas in the left hemisphere exhibit remodelling of language circuitry such that naming tasks recruit not only the usual cortical regions involved in expressive language, but also the entirety of the glioma-infiltrated cortex¹⁰⁵. Secretion of the synaptogenic factor TSP-1 by glioma cells was identified as a key mechanism mediating this remodelling of normal functional circuitry and increasing the responsiveness of glioma cells to neurons¹⁰⁵. Synaptogenic factor secretion is expected to influence not only neuron-to-neuron synaptic connections but also neuron-to-glioma synaptic connectivity. Accordingly, and highlighting the functional importance of neuron–glioma interactions, the degree of functional connectivity between normal brain and adult glioblastoma at the time of diagnosis influences language task performance and is also a powerful predictor of patient survival, with markedly shorter overall survival for patients with glioblastomas that exhibit high functional connectivity¹⁰⁵. Gliomas thus functionally remodel and hijack the neural circuits underlying cognitive domains such as language function¹⁰⁵.

Peripheral nervous system

The peripheral nervous system (PNS), including motor, sensory and autonomic components, innervates organs and tissues throughout the body, releasing neurotransmitters and trophic signals to maintain tissue homeostasis throughout life. The autonomic PNS mediates both adrenergic (sympathetic) and cholinergic (parasympathetic) autonomic responses, producing critical muscle contractions and gland secretions to enable proper visceral organ function¹⁰⁷. Function of the gastrointestinal system is robustly regulated by enteric nervous system (ENS) innervation, including extensive autonomic innervation of the gastrointestinal tract in addition to 500 million enteric neurons located in myenteric and submucosal plexi¹⁰⁸. Peripheral nerves are critical components of the stem cell niches across multiple organ systems and tissue types^{109–114}. For example, fundamental studies by Knox and colleagues have demonstrated the importance of parasympathetic innervation for glandular organogenesis and regeneration¹⁰⁹, including for tubular network and lumen formation during salivary gland organogenesis¹¹⁰. Just as the PNS regulates tissue development, homeostasis and regeneration, recent studies have shown the critical role of peripheral innervation in the progression of various cancers, including prostate, gastric, pancreatic and breast cancers, discussed in detail below. PNS–tumour cross-talk regulates cancer initiation and progression in ways that closely mirror the principles discussed above in CNS cancers (Figs. 4 and 5).

Prostate cancer

The prostate is a densely innervated organ for which both parasympathetic and sympathetic inputs regulate normal prostate growth, homeostasis and function. Early studies using surgical denervation of the prostate demonstrated prominent prostatic atrophy¹¹⁵. Conversely, adrenergic agonists cause prostatic hyperplasia¹¹⁶. These roles for the autonomic nervous system in the regulation of prostate homeostasis and growth suggested that neural elements could have parallel roles in prostate cancer. Concordantly, histopathological analyses of prostate adenocarcinoma identified a phenomenon known as perineural invasion, in which tumour cells invade into and grow along nerves^{117,118}. Retrospective studies examining the clinical and pathological features of patients with

prostate cancer identified increased perineural invasion and diameter of the invaded nerve as an indicator of poor prognosis¹¹⁸. Important early in vitro experiments using a dorsal root ganglion and human prostate cancer cell co-culture system showed that neurons increase prostate cancer cell proliferation, providing some of the first evidence for a growth-promoting effect of neurons on cancer cells¹¹⁹.

A seminal study by Frenette and colleagues provided direct evidence for neural regulation of prostate cancer by both sympathetic and parasympathetic nerves¹²⁰. Ablating adrenergic (sympathetic) nerves chemically or surgically in mouse prostate prevented growth of patient-derived orthotopic prostate cancer xenografts. Further, genetic ablation of β_2 - and β_3 -adrenergic receptors in recipient mice substantially reduced both growth of patient-derived orthotopic prostate cancer xenografts and tumour cell dissemination into the lymph nodes and distant organs. Parasympathetic nerves also influence prostate cancer progression. Muscarinic acetylcholine receptor 1 (Chrm1) signalling in the tumour stroma was found to enhance the dissemination and metastasis of orthotopically xenografted prostate cancer cells. Taken together, these ground-breaking findings from the Frenette group demonstrated the crucial and complex relationship between prostate cancer and the nervous system¹²⁰.

Follow-up studies have implicated additional cellular and molecular components of the nervous system in prostate cancer growth and progression. β_2 -adrenergic signalling promotes vascularization in orthotopic xenograft and MYC-driven genetic mouse models of prostate cancer, in which expression of β_2 -adrenergic receptors on endothelial cells in the tumour stroma decreases oxidative phosphorylation to enhance tumour-promoting angiogenesis¹²¹. Unexpectedly, recent work in a MYC-driven genetic mouse model of prostate cancer demonstrated that doublecortin-positive NPCs migrate from the brain to the prostate cancer niche and generate new adrenergic neurons that then promote prostate cancer initiation and progression¹²².

Gastrointestinal tract cancers

Similar to the prostate and other glandular organs, the gastrointestinal stem cell niche is regulated by extensive innervation, and autonomic nervous system signalling has been implicated as an essential regulator of stem and progenitor cells in the liver^{111,123} and intestinal tract¹¹². The ENS in the gut coordinates with the CNS to regulate gastrointestinal development, homeostasis and function, maintaining a delicate biochemical and immunological balance^{112,124,125}. Underscoring this point, denervation of the stomach leads to profound changes in critical functions such as acid secretion¹²⁶ and gastric mucosal cell proliferation^{127–129}. Nervous system regulation of the gastrointestinal system becomes particularly important in gastrointestinal cancers, in which local nerves affect gastrointestinal tumorigenesis and growth.

Studies have shown enhanced nerve ingrowth in human and murine models of colon adenocarcinoma¹³⁰, further supported by the correlation between nerve density and overall survival in human patients¹³¹. Surgical denervation (vagotomy) of the stomach reduced both the number and size of gastric tumours in a rat model of gastric cancer induced by carcinogen exposure¹³². Pioneering work by Wang and colleagues has illuminated the mechanisms driving this tumour-promoting innervation in a genetic mouse model of

spontaneous gastric cancer. Surgical or pharmacological cholinergic denervation in the pre-neoplastic stage of gastric tumorigenesis clearly demonstrated a critical role for cholinergic innervation in both gastric tumour initiation and progression. Differential gene expression analyses in a vagotomized genetic mouse model of spontaneous gastric cancer showed that Wnt and Notch signalling pathway activity was markedly reduced following vagotomy. Concordantly, cholinergic neuronal signalling to muscarinic acetylcholine receptor 3 (Chrm3) in gastrointestinal cancer stem cells enhances the activity of the downstream Wnt signalling pathway to promote tumorigenesis. The gastrointestinal epithelial tuft cell subtype is the initial source of tumour-promoting acetylcholine in the gastric mucosa¹³³. Production of acetylcholine by these tuft cells drives nerve growth factor (NGF) production in gastric stem cells to promote axonogenesis and further cholinergic nerve ingrowth, with increased acetylcholine release from nerves in the tumour microenvironment. Acetylcholine promotes LGR5⁺ stem cell proliferation through YAP-dependent modulation of Wnt signalling and further increases secretion of NGF in gastric cancer mouse models¹³³ (Fig. 5). Strikingly, increased NGF expression and consequently increased acetylcholine in the gastric stem cell niche is sufficient to induce tumours, whereas NGF–Trk signalling antagonism is robustly therapeutic¹³³. These seminal studies elucidate a direct role for the PNS in shaping the cancer stem cell niche to drive tumour progression in a feed-forward loop of nerve–cancer interactions and represent a clear example of the bidirectional signalling relationships between nerves and cancer cells, as discussed above in glioma (Fig. 1), in which neuronal signalling to cancer cells promotes progression and cancer cells remodel the nervous system to further enhance the pro-tumorigenic signals from neurons (Fig. 4).

In the uppermost part of the gastrointestinal tract, oral squamous cell carcinomas are densely innervated by nociceptive nerves¹³⁴. Oral squamous cell carcinoma cells secrete NGF to promote this innervation of the tumour microenvironment, and nociceptive nerves secrete the neuropeptide calcitonin gene-related peptide (CGRP) to promote cancer growth. The growth-promoting effects of nociceptor-secreted CGRP are mediated by effects on cancer cell metabolism, inducing cytoprotective autophagy in low-glucose environments such as the oral cavity¹³⁴. In preclinical models, the CGRP-blocking migraine medication rimegepant reduced cancer cell autophagy and augmented the therapeutic effects of nutrient-starvation therapies such as anti-angiogenic medications¹³⁴.

Pancreatic cancer

The pancreas is an organ densely innervated by both sympathetic and parasympathetic nerves, coordinating closely with the nervous system to adapt exocrine and endocrine secretions in response to physiological changes^{135,136}. Pancreatic cancer frequently presents with pain, hinting at the connection between pancreatic cancers and the nervous system. Early histological analyses of human pancreatic cancer samples documented prominent perineural invasion in pancreatic ductal adenocarcinoma (PDAC)^{137–139}. Initial correlative studies in human patients also highlighted an association between NGF expression and this perineural invasion, with NGF expression correlating with pancreatic cancer progression and prognosis^{140,141}. More recent studies have identified the critical biological mechanisms that facilitate malignant cross-talk between the nervous system and pancreas in cancer.

Pancreatitis, characterized by increased inflammation in the pancreas, can promote initiation and development of PDAC^{142,143}. Mouse models of pancreatic cancer recapitulate the neuroplastic changes observed in human patients with PDAC and have been used to identify many important transcriptional and neuro-anatomical features present in the early stages of pancreatitis and tumour formation. For example, enhanced expression of TRPV1 and TRPA1 channels, which traditionally have been implicated in neurogenic inflammation, was observed in the sensory neurons of genetic mouse models of PDAC¹⁴⁴. Elevated expression of neurotrophic factors such as NGF and neurotrophic receptors such as TrkB was also observed in the pancreas during these early pathogenic stages of PDAC formation. Further studies in genetic mouse models of PDAC have shown that precancerous inflammation in the pancreas, induced either by repeated injections of cerulein or by *Kras*-driven precancerous inflammatory neoplastic disease (PanIN), causes a substantial increase in CNS glial cell activation and neuronal injury responses¹⁴⁵. Strikingly, capsaicin-induced sensory neuron ablation in these mouse models of pancreatitis abrogated CNS inflammation and reduced pancreatic cancer initiation and progression¹⁴⁵, identifying a role for sensory innervation in pancreatic cancer and demonstrating how peripheral inflammatory signals can be transmitted from the periphery to the CNS through afferent nerves.

Roles have also been clearly demonstrated for the sympathetic and parasympathetic nervous systems in pancreatic cancer (Fig. 5). Catecholamines produced by the sympathetic nervous system, which can be released by local nerves or systemically by the adrenal glands during stress responses, have been linked to PDAC growth in vitro and in vivo^{146–148}, and systemic stress correlates with cancer progression in human patients with cancers of various tissue types, including the bladder, liver, pancreas, stomach, ovary, kidney, breast and lung¹⁴⁹. When chronic stress was induced through a chronic restraint paradigm in a genetic mouse model of early-stage PDAC, levels of β_2 -adrenergic receptors, nerve infiltration and tumorigenesis were enhanced¹⁵⁰. Catecholamines were ultimately shown to directly promote NGF secretion from PDAC cells, leading to increased neurite outgrowth, increased nerve density and accelerated tumour formation.

In contrast to adrenergic sympathetic signalling, cholinergic parasympathetic signalling can suppress pancreatic tumorigenesis. Parasympathetic denervation (vagotomy) increased the incidence of pancreatic tumorigenesis in genetic mouse models of PDAC through expansion of malignant CD44⁺ epithelial cells in the tumour stroma¹⁵⁰. Further experiments in these mouse models of PDAC demonstrated that cholinergic signalling agonists could suppress pancreatic tumorigenesis and prolong survival, primarily through the anti-proliferative effects of Chrm1 signalling in PDAC cells. The role of cholinergic signalling in PDAC stands in stark contrast to its role in gastric and intestinal cancers and underscores the concept that, although the nervous system consistently has important roles in modulating cancer, the role of a particular nerve type or neurotransmitter can vary among cancer types.

Breast cancer

The nervous system similarly has key roles in breast development and cancer. Studies using immunohistochemistry¹⁵¹ and retrograde transneuronal viral tracing^{152,153} have identified prominent adrenergic sympathetic innervation in the mammary gland. Signalling between

mammary gland-derived BDNF and its receptor TrkB on sensory neurons is necessary to establish sensory innervation of the female mammary gland. In males, androgen hormones prevent this BDNF–TrkB signalling axis in sensory neurons, demonstrating a sexually dimorphic mechanism whereby the nervous system directs organ development¹⁵⁴. This cross-talk between breast tissue and the nervous system is maintained in the context of cancer, regulating breast cancer progression.

Analysis of breast cancer specimens from human patients has shown that perineural invasion is positively correlated with disease progression, metastasis and clinical staging¹⁵⁵. Early in vitro studies demonstrated that co-culture of human breast cancer cells and rat neurons resulted in increased NGF production by breast cancer cells and subsequent enhanced neurite outgrowth by the associated nerves¹⁵⁶. Further in vivo work identified sympathetic innervation of breast tumours in humans and in preclinical mouse models of spontaneous mammary tumours¹⁵⁷. Chemical ablation of these sympathetic nerve fibres leads to a decrease in tumour burden¹⁵⁷. Recent work using a retrograde viral vector-based genetic approach manipulated local autonomic nerves in a tumour- and nerve-specific manner to better characterize innervation of the breast cancer microenvironment¹⁵⁸. Specific stimulation of local sympathetic nerve fibres in an orthotopic human breast cancer xenograft model promoted primary breast tumour growth and distant metastasis through locally released noradrenaline. Chemical ablation of the sympathetic nerve fibres in these breast cancer models was shown to reduce immune-suppressive mechanisms, including reduced expression of immune checkpoint signals such as PD-1 and PD-L1 and a decrease in tumour-infiltrating regulatory T lymphocytes. In contrast to local sympathetic nerves, stimulation of parasympathetic nerve fibres in the breast cancer microenvironment decreased primary tumour growth and distant metastasis, as well as suppressed expression of immune checkpoint molecules. Like the role of parasympathetic nerves, destruction of sensory neurons using high-dose capsaicin enhanced breast cancer metastases and promoted a more aggressive gene expression phenotype¹⁵⁹. Taken together, these findings suggest that sympathetic nerves promote breast cancer growth, whereas parasympathetic and sensory nerve mechanisms suppress breast cancer growth, again underscoring the complex regulatory roles that different nerve types can have in specific tumours and highlighting nervous system regulation of the tumour immune microenvironment.

The nervous system also has important roles in regulating breast cancer metastasis. Inducing chronic stress through restraint paradigms substantially increased colonization and metastasis to distant tissues in systemically injected and orthotopic murine models of breast cancer, respectively¹⁶⁰. Blocking β -adrenergic receptors abrogated this stress-induced pro-metastatic switch in orthotopic breast cancer models. Concordantly, pharmacological β -blockade in human patients with breast cancer has been linked to increased immune cell infiltration and a reduction in metastasis-related biomarkers¹⁶¹. Strikingly, macrophages and myeloid cells were found to mediate this stress-enhanced metastatic spread, with stress-exposed breast cancer-bearing mice treated with CSF-1 receptor antagonists to deplete macrophages and myeloid cells no longer exhibiting enhanced metastasis¹⁶⁰.

Basal cell carcinoma

Not all interactions between the PNS and cancer cells hinge on neurotransmitter signalling. Basal cell carcinoma, classically driven by Hedgehog signalling, can arise from various populations of Hedgehog-responsive epithelial stem cells, especially stem cells in the touch dome epithelium¹⁶². Mechanosensory nerves are a major source of Hedgehog ligand in the skin, and nerve-derived Hedgehog ligand drives oncogenic signalling in basal cell carcinoma models (Fig. 2). Concordantly, denervation of the skin strongly abrogates basal cell carcinoma growth in mouse models¹⁶².

Neural regulation of the immune system and tumour immune microenvironment

Neural-immune cross-talk in the local tumour microenvironment

Neural-immune interactions regulate the functions of both systems (for a review, see ref. 163), and cross-talk among immune cells, tumour cells and neurons or neuronal mechanisms can profoundly influence cancer progression (Fig. 3). Prominent examples include the immunomodulatory influence of a range of neurotransmitters that can affect pro-tumour inflammation, anti-tumour immunity or immunotherapeutic effects. For example, adrenergic signalling, derived from local sympathetic nerves or from circulating catecholamines, can exert wide-ranging effects on the tumour immune microenvironment. Noradrenaline signalling, chiefly to the β_2 -adrenergic receptor in immune cells, regulates myeloid-derived suppressor cell states^{164,165}, upregulation of checkpoint molecules such as PD-1 (ref. 166) and T cell exhaustion¹⁶⁷. Adrenergic signalling also limits migration of immune cells in tissues through the effects of sympathetic nerves on vasculature¹⁶⁸. Similar to the effects of noradrenaline from sympathetic nerves, nociceptor sensory nerves promote CD8⁺ T cell exhaustion in the tumour microenvironment of melanoma through release of the neuropeptide CGRP, enabling melanoma progression by impairing anti-tumour immunity (Fig. 2)¹⁶⁹.

In some cases, neuronal mechanisms contribute to cancer pathophysiology in contexts that do not involve neural structures or cells. For example, the neurotransmitter GABA appears to have important roles in multiple cancer types: in primary tumour samples from patients with non-small-cell lung adenocarcinoma or colon cancer, GABA levels increased with tumour stage and inversely correlated with patient survival¹⁷⁰. Autocrine GABA signalling through the GABA_B receptor in colon cancer cells promotes cancer cell Wnt signalling and proliferation while decreasing colon cancer cell expression and secretion of the CCL4 and CCL5 chemokines, thereby reducing tumour infiltration by T lymphocytes and dendritic cells¹⁷⁰. Further implicating GABA in the suppression of anti-cancer immunity, B lymphocyte-derived GABA signals through GABA_A receptors on CD8⁺ T lymphocytes to reduce cytotoxic T cell responses and promote tumour growth in a mouse model of subcutaneous colon adenocarcinoma¹⁷¹. This B cell-derived GABA concomitantly promoted an immune-suppressive phenotype of tumour-associated macrophages in the colon adenocarcinoma tumour microenvironment (Fig. 3). Strikingly, B cell-specific deletion of GABA synthesis through *Gad67* knockout significantly reduced colon adenocarcinoma

growth in this model, demonstrating the important role of neurotransmitters in shaping the tumour immune microenvironment to affect tumour progression.

Serotonin—best known for its roles in the CNS—also has an important immune-modulatory role. Peripheral serotonin is taken up by platelets to influence inflammatory processes and cell proliferation. In the context of orthotopic xenograft mouse models of both gastric and pancreatic cancers, platelet-derived serotonin enhanced tumour growth through PD-L1 upregulation on cancer cells by transglutaminase 2 (TGM2)-mediated serotonylation of histones and consequent epigenetic regulation of immune checkpoint molecule expression¹⁷². In this way, peripheral, platelet-delivered serotonin directly influences CD8⁺ T cell infiltration in these glandular tumours to affect cancer progression (Fig. 3) in a fascinating mechanism at the crossroads of neuroscience, immunology and epigenetics.

Systemic neural–immune interactions

In addition to the examples discussed above in which the nervous system or neuronal mechanisms influence cancer progression through effects on immune cells in the local tumour microenvironment, immune system function can be profoundly influenced at the systemic level by the nervous system (Fig. 4). Such systemic effects, including effects on leukocyte trafficking and function, may influence the efficacy of anti-cancer immunity or immunotherapeutic strategies. The vagus nerve has crucial immunomodulatory roles, not only conveying information about peripheral immune challenges to the brain, but also mitigating inflammatory responses through efferent cholinergic pathways, such as limiting pro-inflammatory cytokine release in experimental lipopolysaccharide (LPS)-induced sepsis¹⁷³. Distinct brain regions and neuronal subtypes orchestrate systemic immune cell trafficking during physiological stress, with the activity of paraventricular hypothalamus corticotropin-releasing hormone neurons and consequent stimulation of the hypothalamic–pituitary–adrenal axis responsible for driving lymphocytes and monocytes from peripheral tissues into bone marrow¹⁷⁴. In health as well as in times of stress, adrenergic signalling and sympathetic innervation of the haematopoietic stem cell niche in bone marrow controls the egress of haematopoietic stem cells into the circulation^{175,176}. Adrenergic signalling also strongly influences immune cell trafficking through lymph nodes¹⁷⁷. Direct innervation of lymph nodes by peptidergic nociceptor sensory nerves modulates leukocyte gene expression in a manner that may influence immune function¹⁷⁸.

Beyond regulating broad shifts in leukocyte population dynamics, the nervous system can encode and retrieve specific immune responses¹⁷⁹. Ensembles of cortical neurons in the insula become active during specific immune challenges, and subsequent stimulation of these specific insular cortex neurons—which project to autonomic nervous system regulatory sites—recreates the immune response operant during the initial inflammatory challenge¹⁷⁹. In this way, the brain can recapitulate a specific immune response through stored neuronal representations of immunological information. How such complex, newly recognized mechanisms of CNS control of immune system function may influence cancer progression or cancer immunotherapy remains to be investigated and may represent important therapeutic opportunities at the intersection of neuroscience, immunology and oncology (Fig. 3).

Conclusions and future directions

Although the field of cancer neuroscience is still in its infancy, pioneering studies have clearly demonstrated the importance of elucidating nervous system–cancer interactions. Building on the foundational discoveries discussed here, progress in cancer neuroscience will benefit from interdisciplinary collaboration among the fields of neuroscience, developmental biology, immunology and cancer biology. As cancers hijack and subvert mechanisms operant during healthy development, insights gleaned from nervous system–cancer interactions are likely to both inform and be informed by mechanisms of development and regeneration.

Targeting nervous system–cancer interactions has the potential to become a pillar of oncological therapy, joining traditional approaches such as surgery, radiation and chemotherapy and the recently codified pillar of immunotherapy. Although targeting nervous system–cancer interactions may not by itself be sufficient to eradicate a tumour, this may be a necessary component of effective therapeutic regimens for currently intractable cancers such as high-grade gliomas and pancreatic cancers.

Intervening on neural mechanisms of cancer growth, spread and therapeutic resistance may leverage existing drugs used in neurology and psychiatry that modulate neurotransmitter receptors, ion channels and other neurophysiological targets. Repurposing existing medication such as anti-epileptic drugs that target neuron–glioma interactions may provide powerful new tools for cancer management. For example, parampanel, which targets AMPA receptors, has demonstrated some promise in preclinical models^{89,90} and early clinical studies¹⁸⁰. However, caution is warranted and preclinical evidence is required before testing a seemingly safe drug in patients with cancer because, whereas some neurophysiological medications may exhibit anti-cancer effects, others may conversely promote progression of a particular cancer. Elucidating the precise neuroscience mechanisms operant in the tumour and tumour microenvironment of each molecularly defined malignancy is of paramount importance to choose helpful medications and avoid potentially deleterious ones.

A number of potential therapeutic interventions have already emerged from preclinical work that may, in clinical studies, be shown to improve cancer outcomes. Strategies to block nervous system–cancer interactions that increase the rate of growth and/or tumour spread may be useful on their own and also complementary to traditional anti-cancer therapies targeting cancer cell-intrinsic vulnerabilities. For each tumour type, it will be important to understand whether nervous system–cancer interactions promote tumour cell survival as well as growth and invasion/metastasis. If it is the case that certain neural–cancer interactions promote therapeutic resistance, combining therapies to block these neural–cancer interactions with cytotoxic therapies such as radiation and cytotoxic chemotherapy may be powerfully synergistic. Blocking neural–cancer interactions that promote tumour growth also may be particularly synergistic with immunotherapies, such as chimeric antigen receptor T cell therapies, for which the rate of immune-based tumour cell killing must outpace the rate of cancer cell proliferation. Furthermore, the recognition that neurotransmitters and other signalling molecules classically associated with the nervous system can directly influence immune cell function highlights the need to study the

influence of neurophysiological medications commonly used to manage seizures, pain, sleep, nausea, anxiety and depression on cancer immunotherapies. Modulating the influence of neurotransmitters and neuropeptides on immune cell function may prove invaluable in overcoming immune-suppressive tumour microenvironments and developing effective immunotherapeutic strategies.

A great deal of work remains to be done in cancer neuroscience, but this avenue of inquiry holds enormous promise to improve outcomes for a wide range of malignancies. At the same time, such inquiry may provide new insights into nervous system regulation of normal organ and immune development, homeostasis and plasticity/regeneration, viewed through the magnifying lens of cancer.

Acknowledgements

M.M. is grateful for support from the US National Institutes of Health, including from the National Institute of Neurological Disorders and Stroke (R01NS092597), an NIH Director's Pioneer Award (DP1NS111132) and the National Cancer Institute (P50CA165962, R01CA258384, R01CA263500, U19CA264504); Cancer Research UK; the Waxman Family Fund; the McKenna Claire Foundation; the Will Irwin Research Fund; and the Virginia and D.K. Ludwig Fund for Cancer Research.

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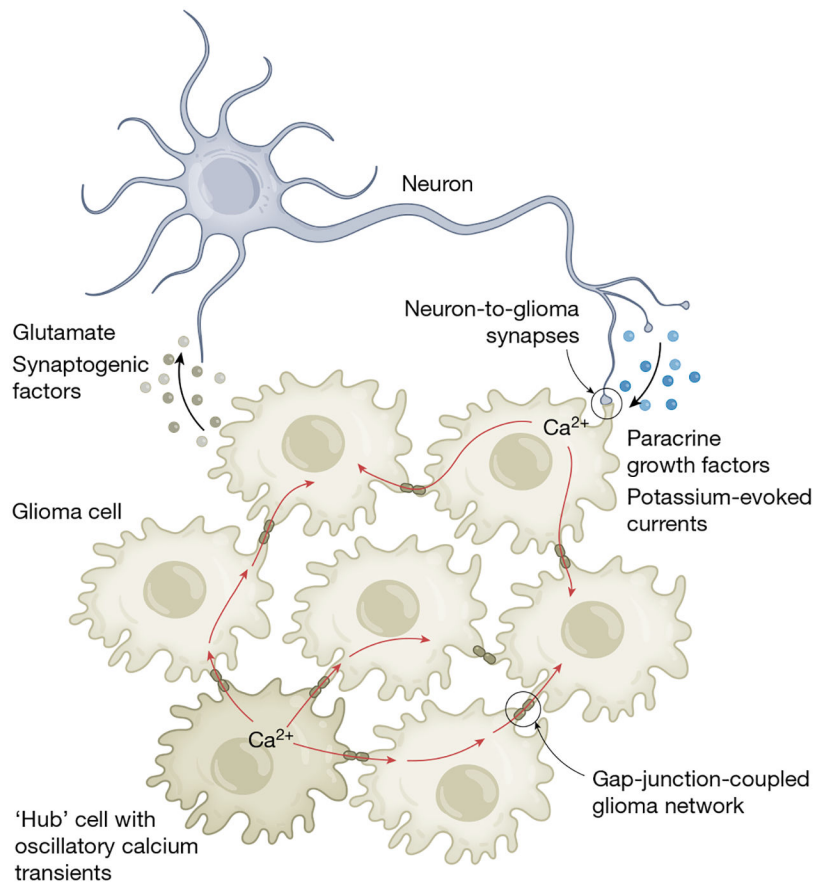


Fig. 1 |. Neuron–glioma interactions in the CNS.

Neuronal activity promotes glioma progression that through activity-regulated secretion of paracrine growth factors, including NLGN3, IGF-1 and BDNF, and by electrochemical communication mediated by synapses between neurons and glioma cells, as well as through potassium-evoked glioma currents. Such electrochemical signals are amplified in a glioma-to-glioma gap junction-coupled network that serves—among other functions—to amplify and synchronize depolarizing currents in the tumour cell network. Membrane depolarization alone is sufficient to promote glioma cell proliferation through voltage-dependent mechanisms that remain to be fully elucidated. ‘Hub’ cells autonomously generate currents that spread through the gap junction-connected tumour network to drive a tumour-intrinsic rhythm of periodic depolarization and consequent calcium transients important for tumour growth. AMPA receptor-mediated synaptic signalling between neurons and glioma cells promotes both tumour cell proliferation and invasion. In turn, glioma cell secretion of factors such as glutamate and synaptogenic proteins (for example, glypican-3 and TSP-1) promotes neuronal hyperexcitability and functional remodelling of neural circuits, thereby increasing neuronal activity in the tumour microenvironment. Glioma-induced increases in excitatory neuronal activity enhance activity-regulated influences on glioma progression. Original figure created with [BioRender.com](https://www.biorender.com).

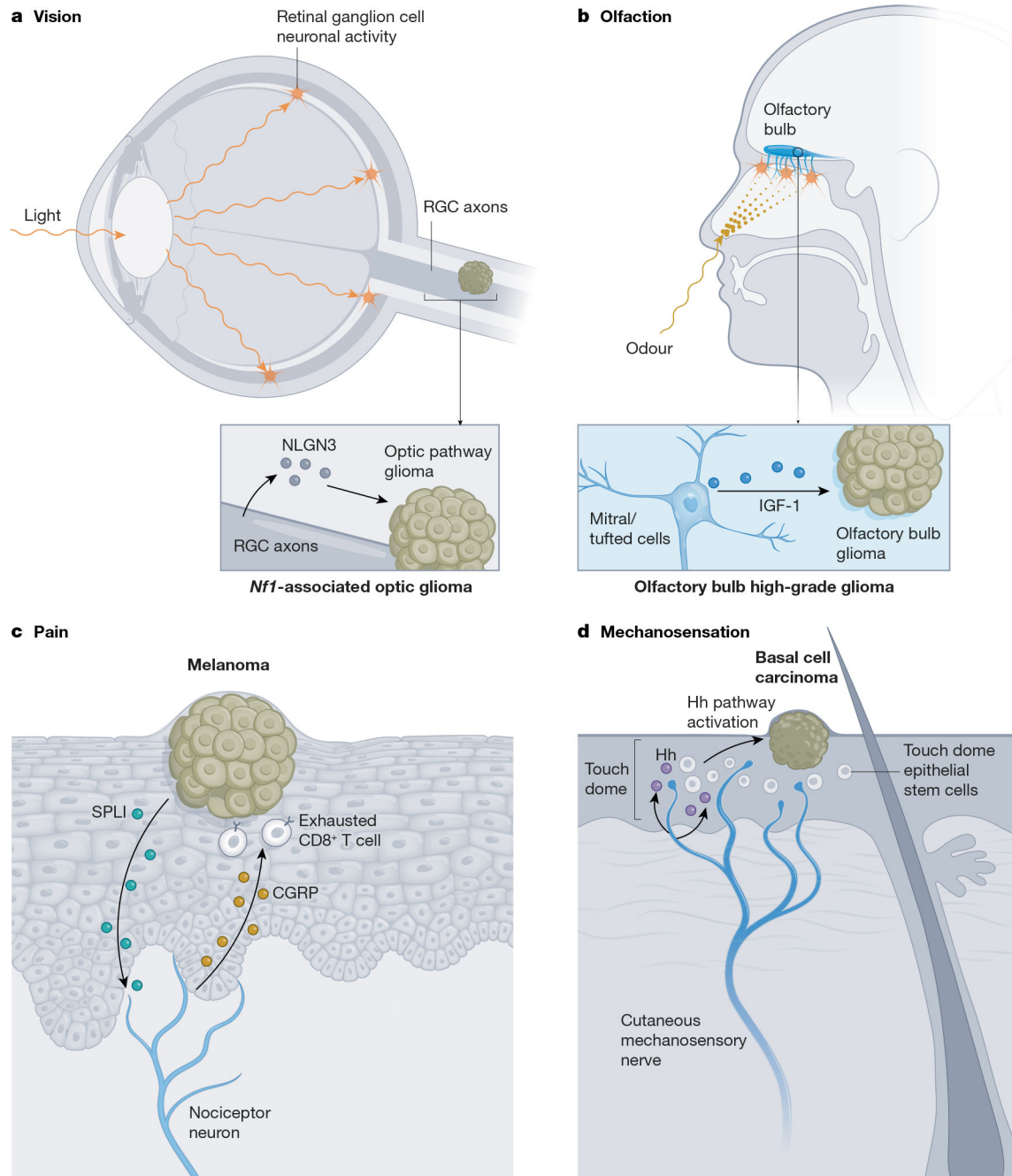


Fig. 2 | Sensory experience and cancers.

a, Visual experience, for example, light, induces activity in retinal ganglion cell (RGC) neurons, whose axons comprise the optic nerve. Optic nerve activity promotes shedding of NLGN3, thereby regulating the initiation, growth and maintenance of low-grade gliomas that occur in the optic pathway in association with the tumour predisposition syndrome NF1.

b, Odorants stimulate olfactory receptor neurons to signal to mitral/tufted cells (a neuronal subtype) in the olfactory bulb, which secrete IGF-1 in an olfactory experience- and neuronal activity-dependent manner, contributing to olfactory bulb high-grade glioma initiation and

growth in a mouse model. **c**, Pain mediated by cutaneous nociceptor nerves in the melanoma tumour microenvironment, stimulated by secretory leukocyte protease inhibitor (SLP1) secreted by cancer cells, results in nerve-derived release of the neuropeptide CGRP. CGRP acts on T lymphocytes to promote T cell exhaustion, thereby limiting anti-cancer immunity and permitting melanoma growth. **d**, Cutaneous mechanosensory nerves innervate the touch dome epithelium, providing Hedgehog (Hh) ligand to touch dome epithelial stem cells, which can give rise to basal cell carcinoma. Mechanosensory nerve-derived Hedgehog ligand induces Hedgehog pathway activity in basal cell carcinoma cells, promoting tumour initiation and growth. Original figure created with [BioRender.com](https://www.biorender.com).

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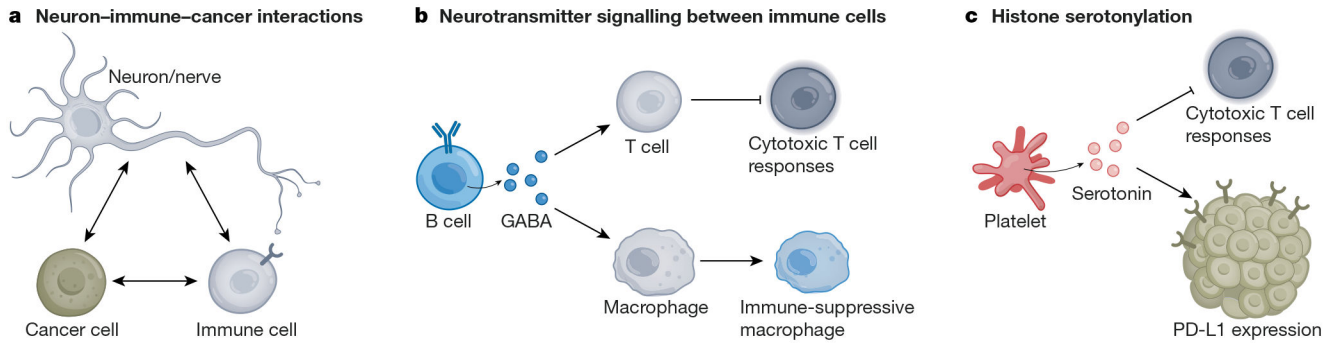


Fig. 3 |. Neuronal mechanisms regulating the tumour immune microenvironment.

a, Extensive cross-talk occurs between neurons/nerves, immune cells and cancer cells.

These interactions can influence anti-cancer immunity and pro-cancer inflammation. **b**,

B cell-derived GABA drives immunosuppression in colon adenocarcinoma. GABA secreted by B lymphocytes binds to GABA_A receptors on T cells to suppress cytotoxic T cell responses and promote an immune-suppressive state in tumour-associated macrophages. **c**,

Serotonin produced by platelets in pancreatic and gastric cancer drives the upregulation of PD-L1 on cancer cells, suppressing cytotoxic T cell responses. Original figure created with [BioRender.com](https://www.biorender.com).

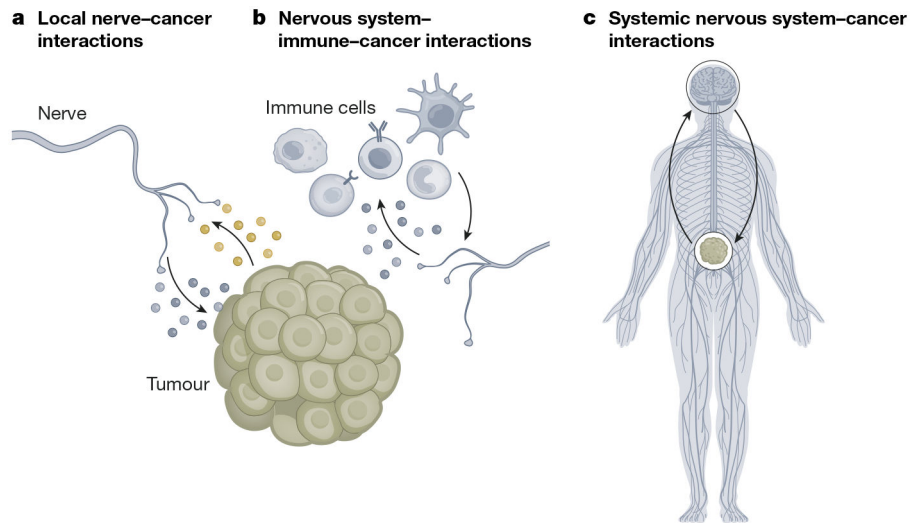


Fig. 4 |. PNS interactions with cancer.

a. Local paracrine signalling from nerves to the tumour or to stromal cells in the tumour microenvironment regulates cancer growth and invasion, while tumour-derived factors remodel peripheral nerves, promoting further nerve ingrowth into the tumour microenvironment. **b.** Nerve-derived factors such as neurotransmitters and neuropeptides can modulate immune cell trafficking and function. Consequently, altered immune function can influence anti-cancer immunity and tumour growth-promoting inflammation. **c.** Systemic interactions between the nervous system and cancers can be mediated by systemic paracrine signalling, for example, circulating catecholamines (including adrenaline), signalling directly to tumour cells or to other cell types in the tumour microenvironment. Reciprocally, tumour cells can influence the nervous system through circulating factors that may in turn regulate such systemic nervous system-cancer interactions (for example, altering the function of the hypothalamic-pituitary-adrenal axis). Original figure created with [BioRender.com](https://www.biorender.com).

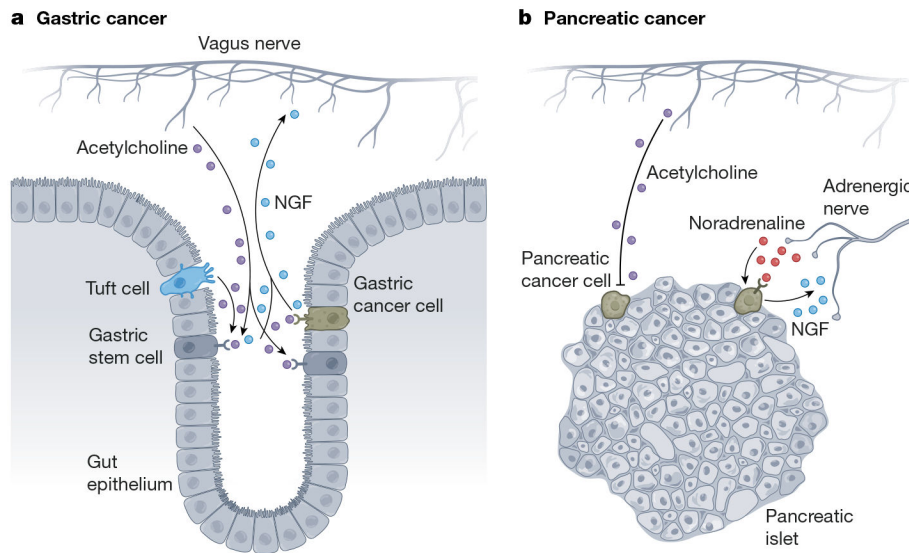


Fig. 5 |. Autonomic nervous system regulation of cancer.

a, Nerve–cancer cross-talk in gastric and intestinal cancers. In gastric cancer, acetylcholine signals to tumour cell muscarinic acetylcholine receptors to promote tumour cell proliferation, while tumour cells secrete axonogenic factors such as NGF to increase nerve ingrowth in the tumour microenvironment. **b**, Nerve-cancer cross-talk in pancreatic cancer. In contrast to its role in gastric cancer, acetylcholine can suppress pancreatic tumorigenesis. By contrast, β -adrenergic signalling (noradrenaline) promotes pancreatic cancer growth, and pancreatic cancer cells secrete NGF to increase sympathetic innervation of the tumour microenvironment. Original figure created with [BioRender.com](https://www.biorender.com).