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REVIEW

Regulation of solid tumors by the peripheral nervous system

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The nervous system has emerged as a critical regulator of cancer progression. Recent studies demonstrate that peripheral neurons shape tumor growth, dissemination, and therapeutic response by regulating multiple components of the tumor microenvironment. In parallel, tumors within the body remodel their neural niche by recruiting innervation and modulating neuronal phenotype and activity. This bidirectional cross talk positions neural circuits as integral components of the tumor ecosystem, linking environmental cues, including metabolic stress, inflammation, and the impact of treatment, to coordinated multicellular responses that promote progression and treatment resistance. Here, we review the field of cancer neuroscience with a focus on solid tumors originating outside the central nervous system. We synthesize mechanistic insights into how the peripheral nervous system shapes the tumor microenvironment to influence tumor behavior and highlight emerging therapeutic opportunities to target neural pathways. Together, these findings identify the nervous system as an upstream regulator of cancer biology and a tractable target for intervention.

Introduction

The conceptual framework of cancer has expanded from a tumor cell–centric disease to one governed by interactions with the microenvironment. While early therapies targeted proliferating tumor cells and later approaches focused on tumor cell–intrinsic signaling pathways, it is now clear that nonmalignant components, including immune and endothelial cells, are critical determinants of disease progression and therapeutic response (de Visser and Joyce, 2023; Tian et al., 2025). This recognition has led to the successful development of therapies that target these compartments, most notably immune checkpoint inhibitors (Sharma et al., 2023). The nervous system is now emerging as an additional layer of regulation. While the presence of nerves within tumors was documented more than a century ago (Young 1897), their functional contribution to cancer is now increasingly recognized. Neural signaling integrates the systemic physiological state of the individual with local microenvironmental cues to coordinate multicellular processes that shape tumor progression and treatment response (Fig. 1).

The nervous system includes the central nervous system (CNS), including the brain and spinal cord, and the peripheral nervous system, which includes sensory, autonomic, motor, and enteric nerves. The CNS integrates and processes information, while the peripheral nervous system mediates communication between the CNS and peripheral organs. Somatosensory and vagal sensory neurons convey information about external stimuli (e.g., sight, touch, and sound) and internal states (e.g., interoception) to the CNS (de Haan and Dijkerman, 2020; Engelen et al., 2023), while autonomic and motor pathways regulate physiological responses in target organs (Wehrwein et al., 2016). Together, these systems coordinate organismal responses to environmental and internal stimuli.

Because the peripheral nervous system also regulates multiple cellular components of the tumor microenvironment, it serves as a key regulator of tumor biology (Fig. 1). A growing understanding of the critical role of neuronal activity in shaping tumor growth, progression, and therapeutic response has given rise to the interdisciplinary field of cancer neuroscience. In this review, we describe evidence that neurons shape tumor architecture by acting on cancer cells, immune cells, and other components of the tumor microenvironment to coordinate accelerated disease trajectory and promote treatment resistance. In an example of bidirectional regulation, tumor cells and stromal cells also remodel the structure and function of tumor innervation, further amplifying neural control of cancer progression and therapeutic response. We focus here on solid tumors that originate outside the CNS and describe the nature and consequences of neural–tumor interactions that occur in these contexts, while also incorporating insights from CNS malignancies and brain metastases (Krishna et al., 2023; Monje, 2025; Venkataramani et al., 2019; Venkataramani et al., 2025; Venkatesh et al., 2019). Understanding these neural–cancer interactions reveals new opportunities to treat cancer by targeting the neural architecture of tumors in the body.

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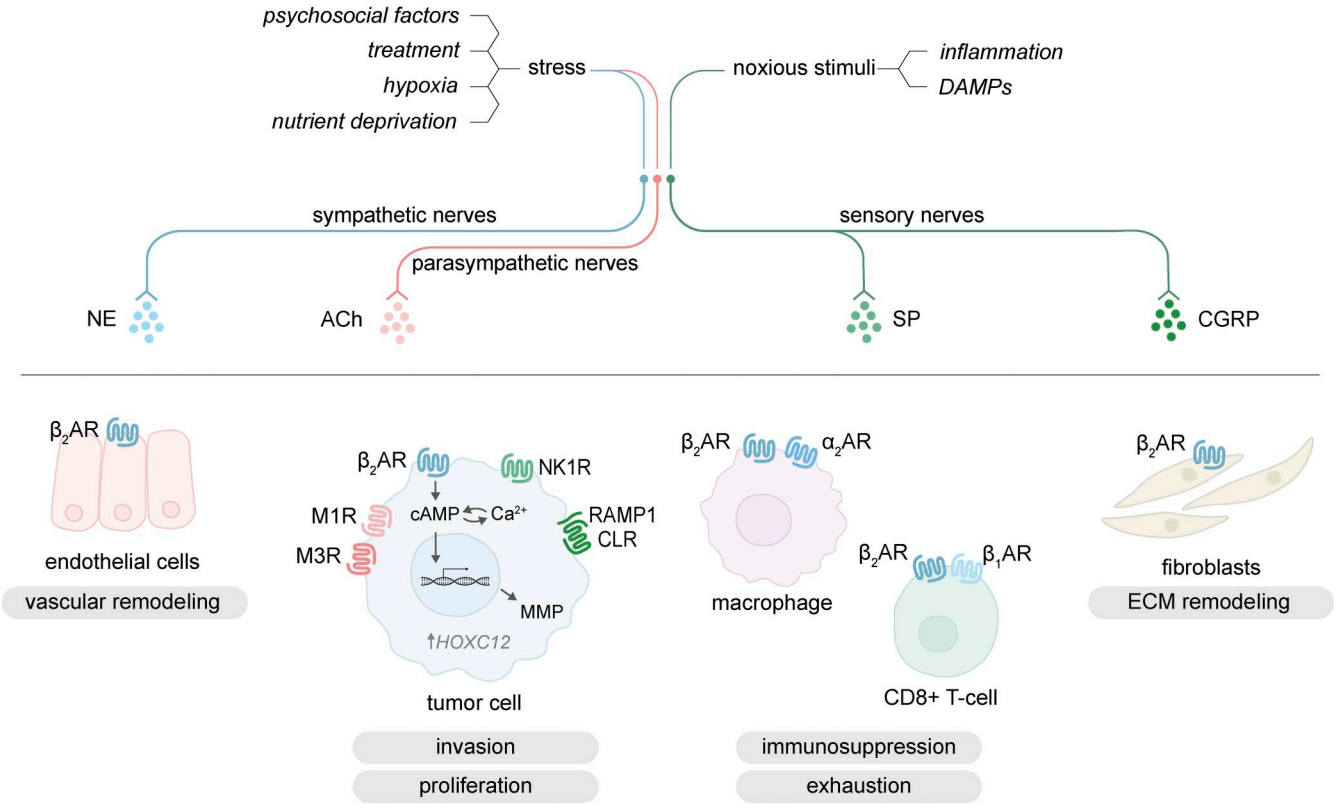

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Figure 1. **Peripheral neural signaling shapes solid tumors.** Solid tumors may be innervated by sympathetic and parasympathetic autonomic nerves, as well as sensory nerves. These neurons release neurotransmitters, including norepinephrine (NE, noradrenaline) and acetylcholine (ACh), and neuropeptides, including substance P (SP) and calcitonin gene-related peptide (CGRP). Tumor cells and nonmalignant components of the tumor microenvironment, including immune cells, endothelial cells, and fibroblasts, express receptors for these neural signals. Through these cellular targets, neural signaling integrates the systemic physiological state of the individual, including responses to cancer treatment, with local microenvironmental cues such as inflammation. The combined neural inputs coordinate multicellular processes that shape tumor architecture, progression, and treatment response. DAMP, damage-associated molecular pattern; α_2AR, α_2-adrenergic receptor; $\beta_{1/2}$AR, $\beta_{1/2}$-adrenergic receptor; M1/3R, M1/3 muscarinic receptor; Ca^{2+}, calcium; MMP, matrix metalloprotease; ECM, extracellular matrix, CLR, calcitonin receptor-like receptor; RAMP1, receptor activity-modifying protein-1.

Neural signaling shapes tumors

Effects on tumor cells

The types of neurons that innervate solid tumors, and therefore the nature of neuronal signaling that cells experience, likely depends on the anatomical origin of the tumor. The sympathetic nervous system and somatic sensory nervous system innervate most organs, and these fibers appear to be present in the majority of solid tumors (Balood et al., 2022; Chang et al., 2023; Chen et al., 2025a; Padmanaban et al., 2024; Renz et al., 2018a; Sakthivelu et al., 2025; Savchuk et al., 2025; Thiel et al., 2025; Zhi et al., 2025). In contrast, parasympathetic innervation is more likely to be present in tumors that arise in the thoracic and abdominal organs as these regions receive vagal innervation, which includes both sensory and parasympathetic fibers (Hayakawa et al., 2017; Peinado et al., 2025).

Neural signaling acts on diverse cellular components of the tumor microenvironment, including tumor cells, immune cells, endothelial cells, and fibroblasts, to induce pleiotropic effects that shape both primary tumors and metastatic lesions. Preclinical studies show that within tumors the sympathetic nervous system predominantly signals through norepinephrine (also known as noradrenaline) acting on β-adrenergic receptors, particularly the β_2-adrenergic receptor (Bucsek et al., 2017; Devi et al., 2021; Globig et al., 2023; Renz et al., 2018a; Sloan et al., 2010; Thaker et al., 2006; Zahalka et al., 2017), although emerging evidence also implicates the involvement of α-adrenergic receptors (Zhu et al., 2023). The sensory nervous system influences tumor behavior largely through antidromic release of neuropeptides: substance P acts via the neurokinin 1 receptor (NK1R), and calcitonin-gene related peptide (CGRP) acts via calcitonin-like receptor/receptor activity-modifying protein-1 (CLR/RAMP1) receptor complexes (Barwell et al., 2012; Steinhoff et al., 2014). In addition, parasympathetic nerves can signal through acetylcholine acting on muscarinic and nicotinic receptors to modulate cells within the tumor microenvironment, particularly in pancreatic, lung, gastric, and prostate cancers (Hayakawa et al., 2017; Magnon et al., 2013; Peinado et al., 2025; Renz et al., 2018b).

Mechanistic studies have expanded our understanding of how the peripheral nervous system regulates tumor cell behavior. Early preclinical work in models of breast and ovarian

cancer identified classical G-protein–coupled receptor signaling pathways downstream of β_2-adrenergic receptors in tumor cells, including activation of cAMP-protein kinase A signaling and Src-regulated invasion pathways (Armaiz-Pena et al., 2013; Creed et al., 2015; Kim et al., 2016; Pon et al., 2016). Signaling via β_2-adrenergic receptors induces cytoskeletal remodeling and protease production, thereby promoting an invasive phenotype (Chang et al., 2016; Kim et al., 2016; Kim et al., 2025; Sood et al., 2006). More recent studies have revealed additional layers of complexity. For example, invasion by triple-negative breast cancer cells requires not only cAMP signaling but also a feed-forward loop of intracellular calcium accumulation that is dependent on homeobox C12 protein (HOXC12) (Lam et al., 2025). Genetic ablation of *HOXC12* in tumor cells abolished calcium amplification, rendering β_2-adrenergic signaling insufficient to drive invasion (Lam et al., 2025). These findings demonstrate that receptor expression alone does not predict functional response to neural inputs and may explain the mixed findings from prior prognostic studies that examined β_2-adrenergic receptor expression in human cancers (Caparica et al., 2020; Caparica et al., 2022; Kurozumi et al., 2019; Liu et al., 2016).

Complexity in signaling also has been identified for sensory neuropeptides in tumors. Substance P promotes invasion via NK1R, and this effect was shown to depend on induction of apoptosis in a subset of cancer cells (Padmanaban et al., 2024). The release of single-stranded RNA from dying cancer cells was found to activate Toll-like receptors, mediating substance P–induced invasion (Padmanaban et al., 2024). Notably, although apoptosis was induced, this did not translate into reduced tumor growth, but instead contributed to a paracrine signaling mechanism that promoted invasion (Padmanaban et al., 2024). These findings highlight that the net outcome of neural signaling within a tumor reflects the integration of multiple processes, including the balance of neural inputs, receptor expression, and coupling to intracellular signaling pathways.

There is growing evidence that the local microenvironment modulates tumor cell responsiveness to neural cues. Consistent with the role of the peripheral nervous system in detecting and responding to environmental changes, stressful microenvironmental states such as nutrient deprivation or exposure to cytotoxic drugs influences neural signaling outcomes (Chang et al., 2023; Zhang et al., 2022). For example, the sensory neuropeptide CGRP increased tumor cell proliferation under low glucose conditions by enhancing autophagy, whereas CGRP had no effect when glucose was abundant (Zhang et al., 2022). These observations suggest that the impact of neural signaling depends on the metabolic features of the microenvironment and that peptidergic sensory nerves may help sustain tumor cell proliferation in nutrient-deprived regions of the tumor. Similarly, exposure to cytotoxic cancer therapies can alter tumor cell responses to sympathetic neurotransmitters. Anthracycline chemotherapy, which is commonly prescribed for hard-to-treat cancers such as triple-negative breast cancer, increased tumor cell expression of β_2-adrenergic receptors and amplified cAMP-mediated invasion signaling pathways (Chang et al., 2023). As patients often receive chemotherapy across multiple treatment cycles, tumor cells that survive a treatment cycle may become progressively sensitized to neural signaling. Because cancer recurrence is associated with treatment resistance and poor survival, it will be important to define how standard cancer therapies used for different tumor types modulate neurotransmitter and neuropeptide signaling.

Neuronal metabolic support of tumor cells

In addition to modulating tumor cells through receptor-mediated actions of neurotransmitters and neuropeptides, there is growing evidence that neurons directly regulate metabolic support for tumor cells. Neuronal inputs can reprogram tumor cell bioenergetics and control the availability of key metabolites, thereby influencing tumor growth and dissemination (Hoover et al., 2025). Neurons have been shown to transfer mitochondria directly to tumor cells, increasing tumor cell stemness and metastatic potential. In experimental models, neuronal mitochondria were transferred to tumor cells in a contact-dependent manner via tunnelling nanotube-like structures. Tumor cells that received neuronal mitochondria had increased metabolic capacity, enhanced resistance to oxidative stress, facilitating metastasis to the brain (Hoover et al., 2025). In clinical prostate cancer samples, tumor cells located in close proximity to nerve bundles contained higher mitochondrial content, and chemical denervation of the prostate using botulinum neurotoxin A reduced tumor cell mitochondrial load (Hoover et al., 2025). While this work has focused on mitochondrial transfer from neurons to tumor cells, other cell types may also contribute to metabolic support within the tumor microenvironment. Immune cells have been shown to transfer mitochondria directly to cancer cells, enhancing oxidative metabolism and tumor progression (Saha et al., 2022). In contrast, satellite glial cells have been reported to transfer mitochondria to neurons in the context of nerve injury (Xu et al., 2026), raising the possibility that glial cells within tumor-associated neural niches could similarly influence tumor metabolism, although this has not yet been demonstrated. Together, these findings suggest that mitochondrial transfer may represent a broader mechanism of metabolic coupling between tumors and their microenvironment. The mechanisms governing this process, including whether it is driven primarily by donor cells, recipient demand, or bidirectional signaling, remain incompletely defined.

Neurons may also provide metabolic support to tumor cells by regulating amino acid biosynthesis and delivery (Banh et al., 2020; Cui et al., 2023). Under conditions of nutrient deprivation, exogenous serine can become rate-limiting for the growth of pancreatic ductal adenocarcinomas (Banh et al., 2020). Sensory neurons can compensate for this deficit by secreting serine from axonal endings in a process that is independent of neuronal firing (Banh et al., 2020). Under conditions of serine deprivation, tumor cells increased secretion of nerve growth factor (NGF), which in turn promoted tumor innervation, suggesting that nutrient stress may select for neuronal metabolic support mechanisms. Additionally, chronic stress was shown to modulate proline biosynthesis and enhance glycolysis in tumor cells, further implicating neural signaling in tumor metabolic pathways (Cui et al., 2019; Cui et al., 2023). These findings suggest

that neurons not only signal to tumor cells but also function as metabolic partners that sustain tumor growth and metastasis under conditions of physiological and therapeutic stress.

Functional synapses between neurons and tumor cells

Nerves in both the peripheral and CNSs have been shown to form synapse-like interactions with cancer cells. Evidence for bona fide synaptic signaling has been demonstrated in the CNS, including in brain metastases where electrophysiological recordings showed postsynaptic currents in tumor cells that are dependent on glutamatergic signaling (Sakthivelu et al., 2025; Savchuk et al., 2025). Outside the CNS, evidence for synapse-like interactions is emerging but remains limited. Recent work has identified synapse-like structures between nerves and tumor cells in peripheral tissues (Ren et al., 2025), although the extent to which these represent functional synapses comparable with those observed in the brain is not yet fully defined. These findings suggest that activity-dependent neuron-tumor signaling may extend beyond the CNS, but further work is required to establish the prevalence and mechanistic significance in peripheral tumors (Peinado et al., 2025).

Nerves shape the tumor microenvironment

In addition to acting directly on tumor cells, peripheral neurons also influence the characteristics of nonmalignant cells in tumors. Immune cells play a critical role in determining the trajectory of cancer progression, and neural signaling is now recognized as an important regulator of anticancer immunity. Both sympathetic and sensory neurons influence innate and adaptive immune responses within the tumor microenvironment and potentially at metastatic sites. Early studies demonstrated that sympathetic nervous system signaling through β-adrenergic receptors promotes myeloid recruitment to tumors and directs macrophage differentiation toward an M2-like phenotype (Lamkin et al., 2016; Sloan et al., 2010). β-adrenergic signaling also increases neutrophil motility and phagocytic activity and suppresses antigen presentation functions of dendritic cells which impairs T cell priming (Nicholls et al., 2018; Nissen et al., 2018). Recent studies show that sympathetic nervous system signaling to $CD8^+$ cytotoxic T cells impairs T cell activation and antitumor effector function (Nissen et al., 2018; Qiao et al., 2019; Qiao et al., 2021). Although much of this work centered on β_2-adrenergic receptors, β_1-adrenergic signaling has also been shown to limit $CD8^+$ T cell proliferation, reduce cytokine production, and promote T cell exhaustion (Globig et al., 2023). Neural regulation of anticancer immunity may have implications for treatment response. In a mouse model of pancreatic ductal adenocarcinoma, tumors responded to immune-checkpoint blockade only when both β_1- and β_2-adrenergic receptors were inhibited, highlighting the functional convergence of these pathways (Globig et al., 2023).

Sensory neurons also exert regulatory effects on $CD8^+$ T cells. In melanoma and oral squamous cell carcinoma, sensory neuron–derived CGRP was shown to promote $CD8^+$ T cell infiltration and exhaustion via the RAMP1 receptor complex (Balood et al., 2022; McIlvried et al., 2022). Ablation of sensory neurons or genetic deletion of RAMP1 in $CD8^+$ T cells diminished exhaustion signatures in T cells within the tumor and reduced tumor growth (Balood et al., 2022).

Beyond the primary tumor, local nerves also may regulate anticancer immunity at metastatic sites. Retrograde tracing studies show that sensory axons innervating both the tumor and its draining lymph nodes share neuronal cell bodies in the trigeminal ganglion, enabling tumor-induced neural activity to propagate to lymphoid tissues (Zhang et al., 2025). Functional studies demonstrated that activation of tumor-innervating sensory neurons induced immunosuppression within the tumor through enrichment of PD-1^+ $CD8^+$ T cells and M2-like macrophages and within tumor-draining lymph nodes through reduced recruitment of T cells and antigen-presenting conventional dendritic cells (Zhang et al., 2025). Chemogenetic inhibition of sensory neurons that innervate draining lymph nodes increased CCL5 levels and shifted macrophage differentiation from an M2 to an M1 phenotype (Zhang et al., 2025). These findings emphasize the importance of examining neural–immune interactions not only within primary tumors but also across local and distant metastatic sites. Furthermore, they demonstrate that neural circuits may allow coordinated responses across multiple organs.

In addition to the direct effects of neurotransmitters and neuropeptides on immune cells, sympathetic neurons regulate anticancer immunity indirectly through their effects on vascular and lymphatic remodeling. Initial studies in ovarian and breast cancer showed that physiological activation of the sympathetic nervous system remodels both blood and lymphatic vessels in primary tumors (Le et al., 2016; Sloan et al., 2010; Thaker et al., 2006). Vascular remodeling involved β-adrenergic modulation of vascular endothelial growth factors-A and -C by tumor cells and macrophages (Le et al., 2016; Sloan et al., 2010; Thaker et al., 2006) and was accompanied by changes in endothelial cell metabolism (Zahalka et al., 2017). Recent studies showed that sympathetic neural control of vascular tone induced tissue hypoxia in lymph nodes, reducing the motility of $CD4^+$ and $CD8^+$ T cells (Devi et al., 2021). As lymph nodes are common sites of metastatic dissemination, reduced T cell motility in this context may impact the ability of T cells to encounter antigen-presenting cells and mount an effective adaptive immune response, with implications for anticancer immunity (Devi et al., 2021). Wholistically, these series of studies demonstrate that neural signaling does not act on tumor cells in isolation, but integrates local environmental cues to coordinate the responses of diverse cell types within tumors.

Tumors shape their innervation

Within the tumor microenvironment, neural architecture is dysregulated compared with adjacent non-tumor tissue and normal, healthy organs (Chen et al., 2025a; Zhi et al., 2025). Several of these altered neural features, including increased nerve density, nerve thickness, nerve injury, and tumor cell invasion of nerves, have been associated with poor cancer outcomes (Amit et al., 2020; Magnon et al., 2013; Pundavela et al., 2015; Schmitd et al., 2022; Xue et al., 2023). Early studies that investigated how tumor cells influence nearby peripheral nerves focused on the stimulating role of tumor cell–derived

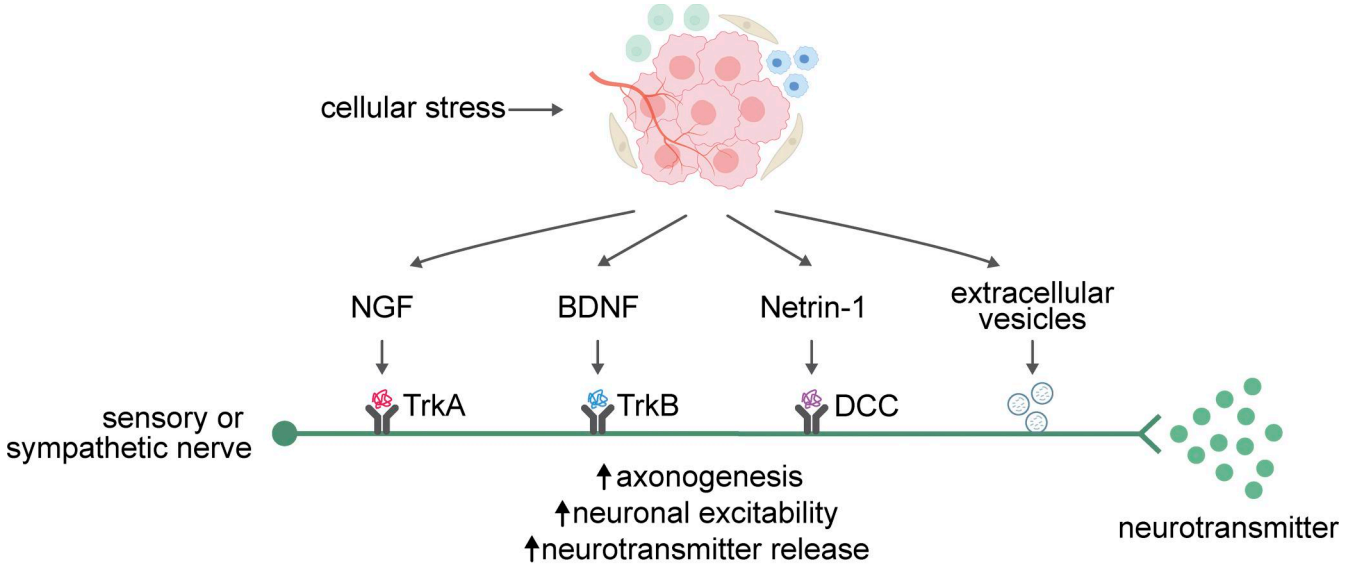

Figure 2. **Tumors shape their innervation.** Tumor cells and stromal cells release neurotrophic factors (nerve growth factor, NGF, and brain-derived neurotrophic factor, BDNF) and axon guidance molecules (netrin-1), which stimulate axonogenesis and modulate neuron excitability and neurotransmitter release. Neurotrophin release may be enhanced by cellular stress induced by treatment or nutrient deprivation. In addition, tumor cells can deliver axon guidance molecules and stimulate axon growth by exosome delivery. DCC, Deleted in colorectal cancer, Trk, Tropomyosin receptor kinase.

neurotrophic factors, including NGF and brain-derived neurotrophic factor (BDNF) (Allen et al., 2018; Pundavela et al., 2015; Renz et al., 2018a). More recent work reviewed here has revealed additional mechanisms involving both tumor cell–secreted and non-secreted factors that support neural remodeling within the tumor microenvironment (Fig. 2).

The majority of current evidence for the origin of tumor innervation supports the idea that nerves within tumors arise predominantly through axonogenesis—the outgrowth of fibers from neurons that are already present in the tissue—rather than through the generation of new neurons (Allen et al., 2018; Balood et al., 2022; Chen et al., 2025a; Pundavela et al., 2015; Renz et al., 2018a). Tumor cells secrete elevated levels of neurotrophins compared to non-transformed cells (Pundavela et al., 2015; Renz et al., 2018a; Zhi et al., 2025), and NGF promotes both sympathetic and sensory innervation of tumors (Chang et al., 2023; Zhi et al., 2025). Genetic deletion of *NGF* in gastric reduced innervation of primary tumors when grown in mice (Zhi et al., 2025). Conversely, overexpression of *NGF* in the gastric epithelium of tumor-free mice increased sensory innervation of the stomach without altering the number of neuronal cell bodies in the jugular ganglion complex or dorsal root ganglia that project to the stomach (Zhi et al., 2025). In addition to neurotrophins, axon-guidance molecules have emerged as important regulators of neural remodeling in tumors. In pancreatic cancer, disruption of tumor cell–derived netrin-1 signaling reduced sympathetic innervation of tumor tissue (Haidar et al., 2025). These findings suggest that tumor cells can actively instruct neural growth through providing guidance cues.

In addition to tumor cells, other components of the tumor microenvironment may contribute to neural remodeling. Immune cells and fibroblasts synthesize and release NGF and BDNF in other contexts, and they may also be a source of stromal-derived neurotrophins in tumors (Kobayashi et al., 2025). Peripheral neurons are often in close proximity with vasculature, forming neurovascular bundles (Malheiro et al., 2021). Endothelial cell–derived Slit guidance ligand-2 (Slit2) has been shown to influence tumor innervation (Padmanaban et al., 2024). Slit2 has been shown to regulate axonal branching through Robo receptor signaling (Ma and Tessier-Lavigne, 2007), although whether this signaling pathway mediates its effect on tumor innervation is yet to be determined. Additionally, neurons themselves also may participate in feed-forward growth loops: β-adrenergic signaling in tumor cells has been shown to induce neuronal BDNF, further supporting axonal growth (Chen et al., 2025b).

In addition to regulation by direct molecular signaling, exosomal communication has also been implicated in tumor innervation. In head and neck squamous cell carcinoma, tumor cells were shown to package the axon guidance molecule ephrin-B1 into extracellular vesicles that potentiated neurite outgrowth (Madeo et al., 2018). Exosomal release by tumor cells appears to be influenced by physiological stress as β-adrenergic receptor signaling increases the abundance of N^6-methyladenosine–modified RNA within exosomes through epigenetic regulation of *ALKBH5*, an RNA demethylase (Chen et al., 2025b). Exosomes containing modified RNA promoted local neurite outgrowth by acting as microRNA sponges within neurons, thereby alleviating repression of gene programs involved in axonogenesis and neural remodeling (Chen et al., 2025b).

External physiological and pharmacological factors can further amplify the ability of tumor cells to promote neural

remodeling. Stress-induced neural signaling through β_2-adrenergic receptors on tumor cells has been shown to increase NGF and BDNF expression (Allen et al., 2018; Renz et al., 2018a). Similarly, exposure to chemotherapeutic agents including doxorubicin and 5-fluorouracil induces neurotrophin expression by cancer cells, through mechanisms including chemotherapy-induced endoplasmic reticulum stress (Chang et al., 2023; Jiang et al., 2022). These studies demonstrate that tumor innervation is not a passive consequence of tissue disruption by a growing tumor, but an actively regulated process driven by tumor-stromal regulation of neural guidance cues, which is sensitive to physiologic stressors and treatments.

Neural differentiation as a source of tumor innervation

Complementing axonogenesis, neural differentiation has been proposed as an alternate mechanism that may contribute to tumor innervation. Tumor-associated neurons could plausibly arise through differentiation of neural stem or precursor cells or via transdifferentiation from other cell types (Amit et al., 2020; Mauffrey et al., 2019). Evidence from oral cavity squamous cell carcinoma suggests that adrenergic tumor innervation may arise from reprogramming of existing sensory innervation (Amit et al., 2020). Tumors harboring mutant but not wild-type *TP53* were reported to secrete extracellular vesicles that promoted neurite outgrowth and norepinephrine release from dorsal root ganglion neurons in vitro, an effect driven by loss of microRNA miR-34a (Amit et al., 2020). Because a subset of dorsal root ganglion neurons express tyrosine hydroxylase (Brumovsky, 2016), the rate-limiting enzyme in catecholamine biosynthesis that was used here as a marker of adrenergic innervation, it will be important to determine whether tumor cell–derived extracellular vesicles induced terminal fate switching or rather enhanced the proportion or functional state of tyrosine hydroxylase-positive sensory neurons through transcriptional reprogramming. Such changes could plausibly increase catecholamine-producing capacity without a change in neuronal lineage.

Brain-resident neural progenitor cells have been proposed as a potential source of tumor-associated neurons in prostate cancer (Mauffrey et al., 2019). The subventricular zone is a neurogenic niche that remains active through the lifespan (Alvarez-Buylla and Garcia-Verdugo, 2002). Using doublecortin-Cre lineage tracing and lentiviral labelling of the subventricular zone, fluorescent doublecortin-positive cells were detected not only within the brain but also within prostate tumors. In addition, fluorescently labeled nerve fibers were observed within tumors, suggesting that they originated from neural precursors that had migrated from the subventricular zone (Mauffrey et al., 2019). These findings have been interpreted as evidence that neural precursors may migrate from the subventricular zone and contribute to tumor innervation (Mauffrey et al., 2019). However, the mechanisms underlying such a process remain unclear. In particular, it is not known how neural progenitors could exit the CNS, survive in circulation, home to peripheral tumors, and functionally integrate into local neural networks. As such, the extent to which neural differentiation contributes to tumor innervation remains to be established. Future studies will be required to determine whether this phenomenon occurs across tumor types and to define the relative contribution of progenitor-derived neurons versus expansion of preexisting axonal networks.

Tumor cells modulate neuron function

In addition to reshaping neural architecture, cancer cells may also modulate the functional state of nerves. Successful innervation requires metabolic support for axonogenesis, neuronal differentiation, and function because the capacity to generate action potentials and propagate calcium waves imposes high energetic demands. Recent studies suggest that tumor cells can direct the differentiation of neural precursors toward a functional neuronal lineage (Hoover et al., 2025). Furthermore, in co-culture with tumor cells, neurons showed expansion of their mitochondrial network, consistent with a metabolic shift from glycolysis toward oxidative phosphorylation (Hoover et al., 2025). Metabolic reprogramming has also been shown in electrically excitable neuroendocrine tumor cells, which adopt neuronal-like programs in small cell lung carcinoma (Peinado et al., 2025). In that context, non-neuroendocrine tumor cells provided metabolic support in the form of secreted metabolites, including lactate and pyruvate, enabling the neuroendocrine cells to undergo a shift toward oxidative metabolism to meet the ATP demand associated with electrical activity (Peinado et al., 2025).

Tumor cells have been shown to modulate the activity of peripheral sensory neurons. In melanoma, tumor-derived secretory leukocyte protease inhibitor (SLPI) increased the excitability of transient receptor potential vanilloid 1 (TRPV1)–positive sensory neurons (Balood et al., 2022). In the absence of tumors, local SLPI injection is sufficient to induce thermal hypersensitivity, indicating sensitization of sensory nerves (Balood et al., 2022). A similar phenomenon was described in oral cancer, in which cancer cells release secreted factors to hypersensitize TRPV1-positive neurons through activation of neuronal protease-activated receptor-2 (PAR_2) and increased local CGRP levels (McIlvried et al., 2022; Scheff et al., 2022). Genetic deletion of PAR_2 diminished the enhanced perception to capsaicin-induced pain by tumor cell secreted factors in mouse models of oral cancer (Scheff et al., 2022).

Tumors may also influence neural activity beyond the primary site. Tumors in the body have been shown to modulate neuronal activity in the brain through both circulating factors and neural pathways. Tumor-derived cytokines, including interleukin-6, can access the brain and modulate defined neuronal populations in the area postrema to regulate systemic physiology, including cancer-associated cachexia (Sun et al., 2024). In parallel, tumor-secreted factors such as leukemia inhibitory factor and galectin-3 have been shown to modulate hypothalamic neurons in the paraventricular nucleus, driving sympathetic nervous system activity that feeds back to regulate tumor progression (Xu et al., 2024).

Complementing these humoral mechanisms, tumor-associated signals can also be transmitted via vagal and somatosensory afferents to brainstem nuclei, including the nucleus tractus solitarius, which project to higher centers such as the

hypothalamus (Gomez et al., 2026; Wei et al., 2026a; Xiong et al., 2023). Through this neural architecture, peripheral tumors engage central circuits that coordinate behavioral, neuroendocrine, and metabolic responses. Consistent with this, tumors in the body can alter hypothalamic circuit activity, leading to changes in circadian and neuroendocrine outputs, including hormonal rhythms (Gomez et al., 2026). In parallel, defined neural pathways that link peripheral tumors to central autonomic circuits can increase sympathetic activity, with downstream effects on anti-tumor immunity and tumor progression (Wei et al., 2026a). At the circuit level, recent work has identified a defined brain–tumor pathway in which tumor-induced activation of corticotropin-releasing hormone neurons in the central amygdala engages a brainstem relay to drive sympathetic outflow to the tumor, thereby modulating intratumoral neural activity, anti-tumor immunity, and tumor progression (Xiong et al., 2023). There is also emerging evidence that after disseminating to the CNS, tumor cells can directly interact with neurons. For example, in models of brain metastasis, small cell lung cancer cells form synapse-like structures with nearby neurons, and in vitro co-culture studies demonstrated increased neuronal activity (Savchuk et al., 2025). These findings highlight that tumors can influence neural function both locally and at a distance through distinct and potentially complementary mechanisms.

Translational cancer neuroscience

The characterization of the nervous system as a key regulator of multiple cellular components of the tumor microenvironment identifies neural pathways as potentially powerful targets for therapeutic intervention. Interventions could conceivably target neurons directly or disrupt receptor-mediated neural signaling within the tumor microenvironment. Targeting the peripheral neural network offers opportunities for both repurposing drugs that were originally developed for neurological indications and for the development of novel tumor-directed therapeutics.

Targeting neurons directly

In principle evidence that the nervous system can be targeted to slow cancer progression comes from in vivo studies that employed chemical ablation of peripheral neurons. Treatment with neurotoxic agents, including 6-hydroxydopamine, capsaicin, resiniferatoxin, or botulinum toxin A, reduced primary tumor growth and metastatic dissemination across multiple cancer models (Balood et al., 2022; Chen et al., 2025a; Magnon et al., 2013; Padmanaban et al., 2024; Sinha et al., 2017; Thiel et al., 2025; Zhao et al., 2014). Although such agents are not likely to be widely used clinically for cancer, these mechanistic studies provide compelling evidence that ablating neurons can improve cancer outcomes.

A more tractable translational approach may involve targeting neurotrophic support for neurons. NGF supports the growth and maintenance of both sympathetic and sensory neurons, and inhibiting NGF signaling via genetic engineering or neutralizing antibodies blocked chemotherapy-induced neurite expansion and suppressed tumor growth in mouse models of breast cancer and other malignancies (Adriaenssens et al., 2008; Chang et al., 2023; Zhi et al., 2025). Anti-NGF antibodies (e.g., tanezumab) were evaluated in clinical trials for osteoarthritis but failed to gain approval from the U.S. Food and Drug Administration, suggesting cancer as a potential alternative indication. Neurotrophic signaling may also be targeted at tropomyosin receptor kinase (Trk) receptors using selective or pan-Trk inhibitors, which have shown efficacy in preclinical cancer models (Adriaenssens et al., 2008; Renz et al., 2018a).

Recent studies also demonstrate the feasibility of repurposing antiepileptic drugs to target CNS activity to control solid cancer that has metastasized to brain. Levetiracetam, an antiepileptic drug, which regulates neurotransmitter release by binding presynaptic vesicle protein 2A, reduced tumor cell proliferation and volume in small cell lung cancer xenografts in the brain (Savchuk et al., 2025). Similarly, riluzole a drug approved for amyotrophic lateral sclerosis, which inhibits glutamate release reduced tumor growth in small cell lung cancer models (Sakthivelu et al., 2025).

In addition to pharmacological approaches, targeted denervation or electrical neuromodulation may offer strategies to limit activity of specific neural circuits. The need for surgery means these interventions would be invasive; however, such approaches could be justified in selected clinical contexts, for example, when denervation is required for pain management. Preclinical studies demonstrated that surgical denervation limits tumor growth (Kappos et al., 2018; Renz et al., 2018a; Renz et al., 2018b; Zhao et al., 2014). Bioelectronic devices that modulate vagal nerve activity are approved for Crohn's disease and treatment-resistant depression and are currently being evaluated in preclinical cancer models (Carreno and Frazer, 2017; D'Haens et al., 2023; Garrett et al., 2025).

Blocking neural signaling within the tumor microenvironment

An alternate and potentially more scalable strategy may be pharmacologic blockade of neural signaling at the level of tumor or stromal cell receptors. The G protein–coupled receptors that bind neurotransmitters and neuropeptides are well characterized and heavily drugged targets, offering substantial opportunities for drug repurposing.

The dominant role of β-adrenergic receptors in mediating sympathetic nervous system signaling in tumors provided a rationale for evaluation of repurposing cardiovascular β-blockers for cancer (Cui et al., 2019; Kim-Fuchs et al., 2014; Sloan et al., 2010; Thaker et al., 2006). Preclinical studies across multiple cancer models demonstrated that β-blockers reduce tumor cell invasion and metastatic dissemination, suppress myeloid recruitment to tumors and T cell exhaustion, and normalize tumor vasculature (Bucsek et al., 2017; Devi et al., 2021; Globig et al., 2023; Kim-Fuchs et al., 2014; Le et al., 2016; Mohammadpour et al., 2019; Qiao et al., 2021; Sloan et al., 2010). Because chemotherapy has been shown to increase the density of tumor innervation, including sympathetic nerves (Chang et al., 2023; Jiang et al., 2022), blocking adrenergic signaling during the treatment window may lead to particular benefit. Consistent with this idea, administration of propranolol concurrent with doxorubicin delayed metastatic onset in mice and was associated

with reduced risk of metastasis and breast cancer-specific mortality in women with triple-negative breast cancer (Chang et al., 2023). Recent prospective, randomized clinical trials have demonstrated the feasibility of combining β-blockers with standard-of-care treatments, including chemotherapy and immunotherapy (Gandhi et al., 2021; Hopson et al., 2021). Although these early-phase trials were not powered to assess cancer-specific survival, transcriptional analyses of tumor samples from breast and colorectal cancer patients treated with β-blockers, either alone or in combination with nonsteroidal anti-inflammatory drugs, showed transcriptional signatures consistent with reduced invasion and restoration of anticancer immunity (Haldar et al., 2020; Hiller et al., 2019; Shaashua et al., 2017).

The β-blocker carvedilol is already used in cancer patients to treat therapy-induced cardiotoxicity, prompting interest in whether it also may improve cancer-related endpoints. Recent preclinical studies showed that carvedilol reduces tumor cell proliferation and tumor growth and metastasis in mouse models of oral squamous cell carcinoma and breast cancer (Amit et al., 2020; Gillis et al., 2021). Retrospective analysis of patients with cardiovascular disorders who were subsequently diagnosed with breast cancer found that those treated with carvedilol tended to have improved breast cancer outcomes, including an almost halving of breast cancer–specific mortality, compared with patients treated with other cardiovascular management strategies (Gillis et al., 2021).

Drugs that target sensory neuropeptide signaling also show promise for cancer. CGRP receptor antagonists are used clinically for migraine and NK1R antagonists (e.g., aprepitant) are prescribed to prevent chemotherapy-induced nausea and vomiting. Preclinical studies demonstrated that CGRP blockade reduces immune-checkpoint exhaustion in melanoma (Balood et al., 2022), while inhibition of substance P signaling through NK1R suppressed breast cancer growth and metastasis (Padmanaban et al., 2024). These findings may have clinical utility. A recent observational clinical study found that aprepitant use during chemotherapy was associated with reduced breast cancer mortality, an effect that was not observed with other antiemetic drugs (Botteri et al., 2025). Together, these preclinical and clinical observations demonstrate the feasibility of targeting neurons or neural signaling pathways to slow cancer progression and improve treatment response. Furthermore, the magnitude of effect suggested by retrospective clinical studies indicates that repurposing drugs that block neural signaling may result in clinically meaningful improvement across selected cancer contexts (Botteri et al., 2025; Chang et al., 2023; Gillis et al., 2021; Løfling et al., 2022; Löfling et al., 2025).

Outstanding challenges and next steps for cancer neuroscience

The expanding evidence linking neural signaling to cancer progression raises a series of questions that will define the next phase of translational cancer neuroscience research. A priority will be to determine the relative impact of neural signaling on cancer across disease stages and through the trajectory of cancer treatment. Accurate translation will depend on establishing when neural signaling is functionally dominant compared with other microenvironmental cues and how this varies across tumor types and therapeutic contexts. In particular, distinguishing cancers that are permissive versus dependent on neural inputs will be essential for rational therapeutic targeting. For example, a recent meta-analysis in breast cancer found that β-blocker use was associated with improved outcomes in triple-negative disease but not in other subtypes of breast cancers (Løfling et al., 2022). The underlying reason is not yet clear and may plausibly be attributed to different biology in triple-negative breast cancers versus other subtypes or the interaction of β-blockers with different standard of cancer treatments used for these diseases.

It will be important for future work to move beyond descriptive associations of innervation toward causal, circuit-level understanding of neural–tumor interactions (Xiong et al., 2023). A range of systemic and environmental signals, including psychosocial stress, inflammation, and tumor-derived factors, can engage central neural circuits that regulate peripheral physiology (Fig. 1). For example, experience of psychosocial stress is processed by limbic circuits, including the amygdala and medial prefrontal cortex, which project to hypothalamic centers such as the paraventricular nucleus (Ulrich-Lai and Herman, 2009). These regions coordinate sympathetic outflow through brainstem autonomic nuclei, ultimately driving adrenergic signaling in peripheral tissues. While this circuitry is well defined in stress biology, its integration into cancer progression remains incompletely understood. Emerging studies suggest that tumors can engage components of these pathways, including hypothalamic circuits that regulate autonomic and neuroendocrine outputs (Gomez et al., 2026; Wei et al., 2026a), but a complete circuit-level framework linking stress, brain activity, and tumor progression has yet to be established.

Once central neural circuits are engaged, an important question is how these signals are conveyed within the peripheral nervous system at the level of specific neuronal subtypes. Advances in single-cell transcriptomics have revealed functional diversity of sensory and autonomic neurons, including the identification of distinct molecular and functional subtypes (Jung et al., 2023; Qi et al., 2024; Wei et al., 2026b). Determining which neuronal subtypes, activity patterns, and neurochemical effectors support tumor growth, immune suppression, and therapy resistance, and in which anatomical contexts, will require integration of neuroscience tools with established cancer models. Parallel efforts to identify biomarkers of neural engagement, such as nerve density, receptor expression, metabolic signatures, or activity-dependent transcriptional programs, will be critical for patient stratification and clinical translation. In addition, emerging evidence of direct interactions between neurons and cancer cells, including metabolic and material transfer (Hoover et al., 2025), highlights an additional layer of complexity that warrants further investigation.

Additionally, it will be important to consider fiscal and policy challenges to translation of repurposed drugs such as β-blockers. Repurposed drugs may offer limited financial return, reducing incentives for late-phase clinical trials, which likely require

large cohorts and extended follow-up periods. As a result, despite the favorable safety profile, global availability, and low cost of agents such as β-blockers, funding for survival-powered trials has been limited (Baker et al., 2025; Lloyd et al., 2025). Overcoming these barriers will be critical for the rapid translation that could be possible for repurposed drugs.

Translating insights from cancer neuroscience into durable therapeutic benefit will require carefully designed interventional studies that consider timing, dose, and combination with existing cancer treatments. Given the availability of clinically approved neuromodulatory drugs and devices, it will be possible to test whether disrupting specific neural–tumor interactions can meaningfully improve treatment response or limit disease progression. Addressing these challenges will determine whether targeting neural regulation becomes a practical component of precision oncology.

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