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Neural regulation in cancer: A comprehensive review from tumorigenesis and progression to immune evasion

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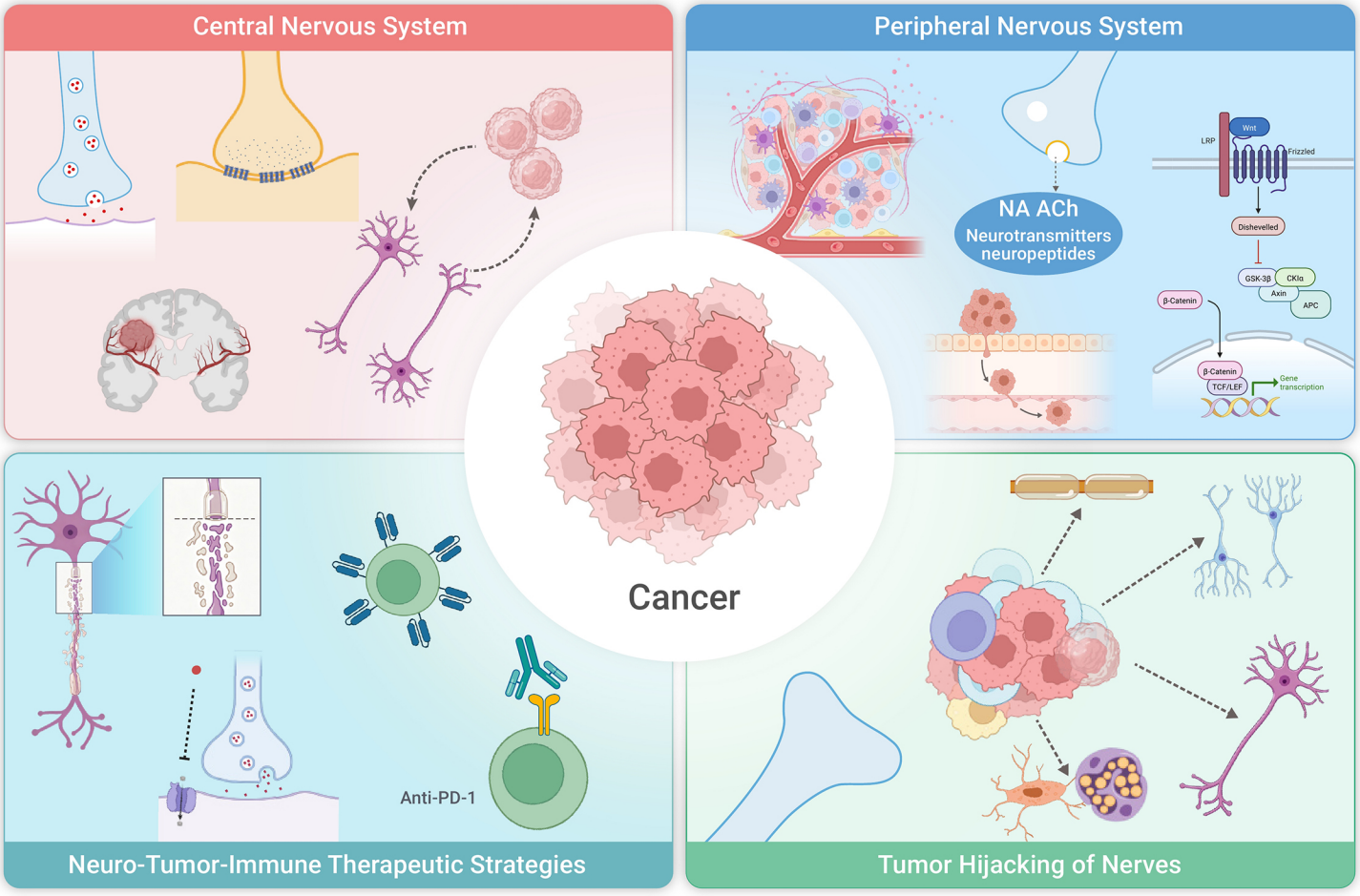
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Nerves actively shape how cancers grow, spread, and evade immune attack.
- Tumors rewire neural circuits and exploit neurotransmitters to create a supportive niche.
- Neural signals alter immune cells, angiogenesis, metabolism, and treatment response.
- Targeting neuro–tumor–immune pathways may enable new combination cancer therapies.

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Neural regulation in cancer: A comprehensive review from tumorigenesis and progression to immune evasion

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Scientific tradition long treated neural and immune activities as essentially separate domains. Contrary to this historical view, studies from the past several decades have fundamentally transformed our understanding. Across various cancers, the nervous system establishes a dynamic, bidirectional regulatory network connecting neural elements, tumors, and immune cells. This occurs through direct interactions (including paracrine communication and electrochemical neuron-cancer signaling) and indirect mechanisms involving the tumor microenvironment (TME) regulation. A two-way regulatory relationship characterizes the nervous system-tumor interaction, combining neural control of oncogenesis with tumor-driven neural plasticity to form a pathological feedback loop. Our analysis delves into how the central nervous system (CNS) and the peripheral nervous system (PNS) directly regulate tumor behavior and anti-tumor immunity, and how cancers hijack normal neural signaling pathways to promote growth and immune evasion. We further examine how tumors and anticancer treatments reciprocally affect neural functionality and immune homeostasis.

INTRODUCTION

Historically, scientists considered neural and immune processes as largely separate domains. The immune system's contribution to tumor initiation and progression is well recognized, and its functions are now regarded as a fundamental hallmark of cancer. By contrast, the nervous system has historically been regarded mainly as a passive recipient of tumor influence, functioning chiefly as a pathway mediating cancer-associated pain and perineural invasion. However, studies over the past few decades have fundamentally overturned this view. Pioneering studies from the late 19th to the mid-20th century provided physiological evidence of tumor innervation.[1] According to a five-year study featured in *Science* in 2013, disruption or chemical inhibition of various peripheral nervous system components considerably reduced or entirely blocked tumorigenesis in prostate cancer mouse models.[2] Neuronal cells can influence tumor cell proliferation, migration, and invasion by releasing neurotransmitters, neurotrophic factors, and other signaling molecules. These interactions are closely intertwined with the formation and regulation of the tumor microenvironment.[3] Through both direct effects—such as paracrine and electrochemical neuron–cancer communication—and indirect effects mediated by modulation of the tumor microenvironment, the nervous system forms a complex, dynamic, and bidirectional regulatory network comprising nerves, tumors, and immune cells across various malignancies.[4]

A bidirectional regulatory relationship exists between the nervous system and tumor, with neural control of oncogenesis existing alongside tumor-induced neural plasticity, together fostering a pathological feedback loop. This reciprocal interaction not only induces neural dysfunction but also drives malignant tumor growth. Tumor cells release neurotrophic factors, axonal guidance factors, vascular endothelial growth factor (VEGF), and various chemokines that collectively stimulate axon formation, neural growth, and the development of new blood vessels.[5] These neuro–immune interactions are crucial determinants of therapy resistance and the coordinated dynamics within cancer cell populations.[6]

In this article, we examine in depth how CNS and PNS regulate tumors through direct communication (e.g., synapses) and paracrine signaling, and how tumor cells "hijack" the normal physiological pathways of the nervous system to facilitate their own growth and immune evasion. Furthermore, we discuss how tumors and anticancer treatments exert feedback effects on neural function and immune homeostasis. Understanding this intricate interaction network will provide a theoretical foundation for creating innovative neuro–tumor–immune therapeutic strategies.

COMPOSITION AND FUNCTIONS OF THE NERVOUS SYSTEM

The nervous system is composed of diverse populations of neurons and glial cells, whose branches extend into nearly all tissue microenvironments except for keratinized structures.[7] Beyond its recognized involvement in sensory perception, movement, and cognitive activity, the nervous system plays a central role in regulating tissue and organ development, adaptation, plasticity, and repair. From a structural perspective, the nervous system is divided into the CNS and the PNS. Serving as the body's principal control unit, the CNS is responsible for synthesizing sensory inputs, managing motor activity, and supervising cognitive and emotional regulation. The PNS, which includes all nerves outside the CNS, innervates organs and tissues throughout the body to maintain tissue homeostasis. In addition, the enteric nervous system (ENS) governs the gastrointestinal tract's neural functions. Its composition includes elements from both the autonomic and somatic nervous systems.[8] However, due to its complexity and its capacity to operate independently from the CNS and PNS, it is often regarded as a distinct system in its own right.[8,9]

CENTRAL NERVOUS SYSTEM

Development, plasticity, and regeneration of the central nervous system

During neural development, the CNS neurons originate from neuroepithelial cells of the ectodermal neural plate.[7,9] As the neural plate undergoes folding to give rise to the neural tube, it further develops into the CNS. A coordinated series of events underlies this process: neural stem and progenitor cells give rise to neurons and glial cells, which then differentiate, mature, and migrate to specific locations. Subsequently, functional circuits are assembled via axonal guidance, synaptogenesis, and the formation of myelinated sheaths that enable swift neural transmission.[7]

Throughout the CNS development, astrocytes, the most abundant glial cell type, perform numerous functions essential for health, development, and injury response,[10] particularly in synaptogenesis.[11,12] Similarly, oligodendrocytes—especially oligodendrocyte precursor cells (OPCs)—play a key role in CNS myelination.[13] From the initial neural induction in embryogenesis to the adaptive plasticity of mature brain networks, every phase of neural development is modulated by neuronal activity.[14] At the synaptic level, this activity—characterized by neurotransmitter release and postsynaptic depolarization—triggers voltage-gated calcium entry that subsequently regulates diverse cellular processes.[7]

Neuronal activity remains a principal regulator of cellular plasticity across

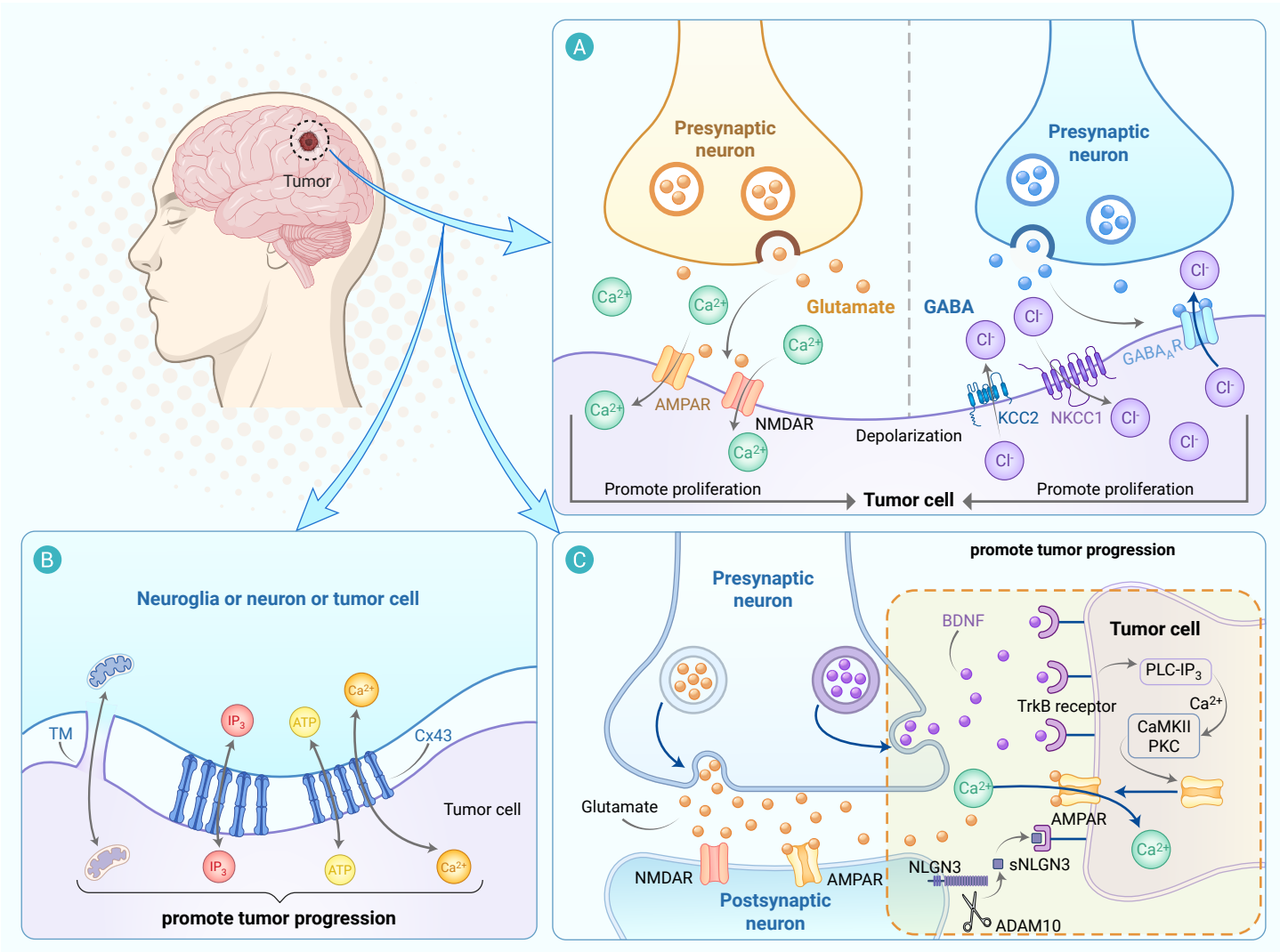

Figure 1. Neural regulation of central nervous system tumors (A) Direct synaptic communication between neurons and tumor cells: Glutamatergic neurons can form bona fide synapses with high-grade glioma cells. These synapses primarily signal through calcium-permeable AMPA receptors, inducing membrane depolarization and Ca^{2+} signaling and thereby promoting tumor-cell proliferation and invasion. In H3K27M-altered diffuse midline glioma, GABAergic neurons can form functional GABAA receptor-mediated synapses with tumor cells. NKCC1 maintains a relatively high intracellular Cl^- concentration, such that activation of GABAA receptors triggers Cl^- efflux and membrane depolarization, ultimately promoting tumor-cell proliferation. (B) Tumor microtube-mediated glioma networks and mitochondrial transfer: Glioma cells can extend tumor microtubes, which contribute to tumor invasion and connect spatially distant tumor cells. At sites of cell-cell contact, interconnected tumor microtubes form connexin 43 (Cx43)-mediated gap junctions, supporting the propagation of Ca^{2+}-associated activity and other small-molecule signals throughout the tumor network. In addition, astrocytes can transfer intact mitochondria to glioblastoma cells through GAP43-positive, actin-dependent tumor microtube-like connections, thereby enhancing oxidative metabolism, proliferation, and tumorigenic capacity in recipient tumor cells. (C) Neuronal activity-dependent paracrine regulation: Neuronal activity promotes the secretion of brain-derived neurotrophic factor (BDNF) and induces ADAM10-mediated cleavage and release of neuroligin-3 (NLGN3). BDNF-TrkB-CaMKII signaling promotes the membrane trafficking of AMPA receptors and strengthens neuron–glioma synapses. ADAM10 cleaves membrane-bound NLGN3 from the surface of neurons and oligodendrocyte precursor cells, releasing soluble NLGN3, which in turn promotes glioma growth and synapse formation.

the entire lifespan, a role that is established during developmental stages. Activity-dependent processes drive adult brain plasticity and adaptability, prominently through the continuous generation and remodeling of myelin. Motor function, skill acquisition, attentional processes, short-term and consolidated memory, as well as social conduct, are all influenced by this capacity for dynamic myelin remodeling.[15] Although the human CNS possesses limited self-repair and regenerative capacity during early development, this ability declines sharply after birth. Consequently, neurodegenerative diseases and certain physical injuries often result in irreversible CNS damage and functional loss.[16]

Regulation of tumors by the central nervous system

Direct dialogue between neurons and tumor cells. During development, neuronal synaptic activity and membrane-tube-mediated cellular networks both contribute to synchronization and signal amplification through distinct mechanisms. However, in the context of tumorigenesis, these same processes can paradoxically support tumor proliferation (Figure 1).

The role of direct synapses in neuron-tumor cell signaling. In the CNS, glutamate is the primary excitatory neurotransmitter. Glutamate receptors are mainly divided into two categories: metabotropic glutamate receptors (mGluRs), which are G-protein-coupled, and ionotropic glutamate receptors (iGluRs). The latter include NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate), and Kainate receptors.

Evidence from electron microscopic, electrophysiological, and calcium imaging analyses confirms the presence of functional glutamatergic synapses linking neuronal and glioma cells in high-grade gliomas.[17,18] These synaptic structures promote tumor proliferation through AMPA receptor– and BDNF–TrkB–dependent signaling.[19,20] For instance, when glutamatergic neurons release glutamate, glioma cells receive the signal through AMPA receptors, inducing Ca^{2+} influx that enhances tumor invasiveness while also regulating glioma initiation and maintenance.[21,22]

Beyond passively receiving signals, brain tumors can actively remodel synaptic structures by exploiting the molecular toolkit normally used for synapse formation between neurons, thereby integrating themselves into

neural circuits.[17] Remarkably, gliomas can prune nearby synapses to optimize their own "signal reception," a form of synaptic plasticity that may explain why certain antiepileptic drugs exhibit anti-tumor properties.[19]

In metastatic brain tumors, such as breast cancer brain metastases, invading cancer cells replace astrocytes at neuronal synapses to establish NMDA receptors (NMDAR)-dependent colonization. These metastatic cells mimic astrocytes to form pseudo-tripartite synapses, supplying glutamate ligands that activate NMDAR signaling and stimulate intracranial tumor growth.[23] Similarly, recent findings indicate that small cell lung cancer (SCLC) "hijacks" synaptic signaling—particularly glutamatergic pathways—to drive disease progression. This study provided the first evidence that peripheral tumors can form functional synapses with neurons, thereby reshaping our understanding of neuro-tumoral communication and offering new therapeutic targets for SCLC.[24]

γ-Aminobutyric acid (GABA), the brain's major inhibitory neurotransmitter, exerts its effects through ionotropic $GABA_A$ and $GABA_C$ receptors, as well as metabotropic $GABA_B$ receptors.[25] In low-grade gliomas, reduced expression of GABA receptors diminishes inhibitory regulation on tumor growth.[26] Emerging research indicates that sodium–potassium–chloride cotransporter 1 (NKCC1) and potassium–chloride cotransporter 2 (KCC2) are key mediators of the neuronal hyperexcitability associated with tumors. Specifically, malignant gliomas upregulate NKCC1 expression in neighboring neurons, leading to intracellular chloride accumulation and reversal of the chloride gradient.[27] Consequently, GABA binding triggers chloride efflux and membrane depolarization, paradoxically promoting excitation rather than inhibition.[28,29]

Current evidence suggests that targeting specific glutamate/GABA receptors, postsynaptic signaling pathways, or mechanisms essential for synaptogenesis may represent promising therapeutic strategies to suppress *tumor p*roliferation.[17,23,24,30]

Membrane tube connections in brain tumors. In recent years, in vivo two-photon microscopy under chronic cranial-window conditions in mice has revealed a unique class of elongated, highly functional membrane protrusions within gliomas that interconnect tumor cells throughout the brain.[31] These structures, termed "tumor microtubes" (TMs), have emerged as critical mediators of glioma cell communication, transport of material, and collective behavior.[32,33]

TMs exist in two main subtypes: non-connected TMs and interconnected TMs. Non-connected TMs primarily facilitate glioma invasion, while interconnected TMs form networks composed of homogeneous glioma cells or hybrid glioma–astrocyte structures linked through multiple intercellular coupling mechanisms.[34] Both subtypes contribute substantially to malignant glioma progression. Recent studies have demonstrated that glioma cells can incorporate mitochondria from non-tumor astrocytes through a growth-associated protein 43 (GAP-43)-dependent mechanism that drives TMs formation.[35] The transfer of mitochondria enhances metabolic activity and tumorigenic potential.

Accordingly, therapeutic targeting of these structures differs by subtype. For non-connected TMs, the principal objective is to suppress invasive behavior. Agents such as Y-27632 and IMM-02 can Successfully block TM-mediated invasion and reduce glioma cell motility.[34] Therapeutic approaches targeting interconnected TMs, however, aim to dismantle their networking capabilities. This is primarily achieved by suppressing calcium-wave transmission and uncoupling gap junctions. Destruction of connexin 43 (Cx43), a key component of these junctions, has been shown to sensitize glioma cells to both radiotherapy and chemotherapy.[35]

Indirect regulation by neural paracrine factors. In addition to direct synaptic connections, the CNS regulates the tumor microenvironment and immune responses through neurotransmitters and neurotrophic factors that act in a paracrine manner. This mechanism is a major contributor to the immune evasion observed in brain tumors.

Neurotransmitter. Neurotransmitters can drive tumor development via autocrine and paracrine signaling. Non-synaptic glutamate secretion supports glioblastoma cell survival, proliferation, and migration by functioning as a trophic factor. When extracellular glutamate concentrations reach excitotoxic levels within peritumoral tissue, tumor progression and tumor-associated epilepsy are promoted.[26] The fundamental mechanism entails aberrant signaling through neuronal glutamate receptors, with NMDAR overactivation playing a prominent role. This results in sustained intracellular calcium elevation,[36] excitotoxicity, and the subsequent generation of physical space that facilitates tumor expansion.[37] Using a soft-matrix mixed glial cell culture (MGS) model, researchers discovered that astrocyte-derived Wnt-5a induces mGluR1 expression in cancer cells. mGluR1 stabilizes EGFR in a glutamate-dependent manner, thereby activating human lung cancer brain metastases.[38] Consequently, targeting mGluR1 presents a potential treatment avenue for patients with EGFR-mutant lung cancer and associated brain metastases.

GABA, on the other hand, is abundantly taken up and utilized by glioma cells through metabolic reprogramming, serving as an energy source and substrate for the tricarboxylic acid cycle to promote proliferation.[39] Furthermore, $GABA_A$ receptor activation induced by glutamate transaminase 2 (GPT2) increases Ca^{2+} influx[40] via calcium channels, activating the PKC–CREB pathway. Activated CREB enhances the expression of metastasis-related genes (such as PODXL, MMP3, and MMP9),[41] thereby accelerating breast cancer metastasis,[40] representing a potential therapeutic target.

Dopamine (DA) exerts either promotive or inhibitory effects on tumor growth by binding to its different receptors.[42,43] Among the five dopamine receptors, DRD2 is the most frequently studied.[44] In one study, we found that chronic stress-induced depression promotes the progression of glioblastoma (GBM) and reduces the median survival of tumor-bearing nude mice and immunocompetent mice. Following chronic stress, levels of DA and its receptor DRD2 significantly increased in GBM tissues. This upregulation jointly mediated the promotive effect of chronic stress on glioma malignancy via the DRD2/ERK/β-catenin pathway and the dopamine/ERK/TH regulatory circuit. Notably, in GBM patients with depression, tumor tissues showed significant upregulation of DRD2 and β-catenin, which was negatively correlated with patient prognosis.[45] Consistently, our results demonstrate that the combination of the specific DRD2 inhibitor pimozide (PIMO) with temozolomide (TMZ) exerts stronger anti-tumor effects in GBM.

Neurotrophic factors and synaptic adhesion factors. Neuronal activity stimulates the release of brain-derived neurotrophic factor (BDNF).[46,47] Within a healthy cerebral environment, BDNF fosters adaptive plasticity through its modulation of synaptic efficacy and network integration.[48–50] Both neurons and tumor cells can secrete BDNF, which activates downstream signaling through its receptor TrkB, enhancing tumor cell invasion and therapeutic resistance. Within gliomas, BDNF acts to promote synaptogenesis, thereby elevating the quantity of synaptic connections between neurons and tumor cells.[20] Moreover, BDNF facilitates AMPA receptor trafficking to glioma cell membranes, strengthening neuron–tumor synaptic signaling and promoting high-grade glioma proliferation.[33] The use of a Trk inhibitor to block BDNF secretion regulated by neuronal activity has been demonstrated to significantly reduce the growth of high-grade glioma cells.[51]

The postsynaptic adhesion protein, NLGN3, which is fundamental to synapse formation and function, has been identified as a principal contributor to tumor advancement.[52] Cleavage of NLGN3 by the metalloprotease ADAM10 in an activity-dependent manner enhances glioma cell growth.[53,54] In mouse models, inhibition of ADAM10 markedly reduced both high- and low-grade glioma growth.[55] This mechanism enables neuronal activity to remotely influence glioma growth and microenvironmental remodeling, while cancer cells hijack the NLGN3 signaling pathway to support their expansion.[52]

Furthermore, GBM-derived NLGN3 exhibits oncogenic properties: its overexpression endows adjacent cells with cancer stem cell (CSC) characteristics.[52,55,56] Conditioned media containing NLGN3 or recombinant NLGN3 induces CSC-like traits in neighboring cells, confirming that NLGN3 is a key factor in CSC induction[57]. Targeting NLGN3-positive CSCs using Wnt/β-catenin[58] inhibitors enhances the efficacy of conventional therapies, suggesting a novel therapeutic strategy to improve GBM outcomes.[57]

Growth-regulating growth factors. Midkine (MDK), a pleiotropic paracrine growth factor,[59] induces T cell secretion of CCL4 and promotes microglial release of CCL5, both of which are mitogenic for glioma cells.[60–62] In optic glioma, NF1 mutation–induced neuronal hyperexcitability increases MDK production via HCN1 channel dysregulation.[63] Accordingly, the antiepileptic drug lamotrigine,[64] which targets HCN1 channels, normalizes MDK expression and suppresses NF1-associated glioma proliferation.[21]

More recently, insulin-like growth factor 1 (IGF-1) has been recognized as an additional activity-dependent paracrine mediator that links olfactory stimulation to the initiation of gliomas within the olfactory bulb.[22] These data confirm a crucial mechanism for IGF-1 signaling in gliomagenesis and progression, offering a potential therapeutic direction for glioma treatment.

The interplay between the central nervous system and tumor immunity

Traditionally, the CNS was regarded as an immune-privileged compartment, a view supported by early observations of absent conventional lymphatic drainage and the lack of immune rejection following intracerebral skin graft transplantation. The perceived immune isolation of the CNS was additionally linked to the protective role of the blood–brain barrier and the immunosuppressive activity of local microglia.

It is now established, however, that the CNS is not an absolute immune sanctuary but rather hosts a dynamic immune landscape. Immune compartments of the brain—encompassing the parenchyma and border-associated immune niches such as the meninges, choroid plexus, and perivascular spaces—support the infiltration and residence of immune cells, which play central roles in CNS physiology.[65] For instance, microglia, the innate immune cells resident in the brain, respond rapidly to ischemic injury; upon activation, they secrete various chemokines and are critically involved in modulating neuroinflammation.[66] Furthermore, peripheral immune cells can access the CNS immune environment via highly permeable circumventricular organs—which contain fenestrated capillaries—or when the blood-brain barrier is compromised, making these routes vital hubs for neuroimmune communication.[65]

Brain-region-specific regulation of tumor immunity. CNS tumors, particularly high-grade gliomas such as glioblastoma, are malignancies with extremely poor prognosis. Despite advances in surgery, radiotherapy, and chemotherapy, patient survival remains limited. The tumor heterogeneity, blood-brain barrier, and a highly immunosuppressive tumor microenvironment represent major obstacles to effective treatment. Over the past decade, research has increasingly demonstrated that CNS tumors are not isolated entities but engage in dynamic and complex crosstalk with the host brain environment—particularly with neural circuits and the immune system. This integrated neuro–immune network serves as a principal regulator of tumor triggering, progression, and resistance to therapy.

Emerging immunotherapeutic[66–70] modalities-including chimeric antigen receptor (CAR) T-cell therapy, therapeutic use of oncolytic viruses, therapeutic cancer vaccines, and immune checkpoint inhibitors—have exhibited substantial efficacy in preclinical investigations of primary CNS neoplasms, notably high-grade gliomas, treatment-refractory embryonal brain tumors, and primary CNS lymphomas. However, their clinical translation has faced significant challenges. A major challenge lies in the highly immunosuppressive characteristics of CNS tumors, which attract myeloid-derived suppressor cells (MDSCs) to remodel the tumor microenvironment and secrete cytokines, chemokines, and diverse signaling mediators that facilitate neoplastic progression.[71,72]

Furthermore, the nervous system naturally restrains lymphocyte-driven inflammation as a protective mechanism against autoimmunity, through the recruitment of MDSCs and regulatory T cells (Tregs), along with the secretion of immunosuppressive cytokines.[73] Analogously, neuro-immune-tumor interactions can dampen responses to immunotherapy. Consequently, targeting these multifaceted interactions represents a critical future direction for improving brain tumor treatment.[74]

Intervening at brain borders in tumor immunity. As previously discussed, the CNS exhibits distinct immunological mechanisms that mirror the intricate nature of its constituent tissues, rather than signifying an absolute state of immune privilege.[75] Recent studies underscore the critical function of specialized compartments at the brain's interface, such as the meninges, choroid plexus, perivascular spaces, cranial and vertebral bone marrow, and CNS-draining lymph nodes,[76–81] in facilitating immune surveillance of the CNS.[81,82]

Studies have shown that enhancing tumor antigen drainage via meningeal lymphatic vessels (MLVs) can potentiate immune-mediated rejection of CNS tumors.[83] The transport of CNS-derived macromolecules and immune cells to cervical lymph nodes (CLNs) is facilitated MLVs located on the dorsal and basal surfaces of the dura mater. Given this role, MLVs represent a potential therapeutic avenue for a range of neuroinflammatory and neurological disorders.[84] The function of MLVs in draining brain tumors and modulating antitumor immune responses is an area of growing interest.[83,85] Studies demonstrate that specifically impairing dorsal MLVs—while leaving basal and nasal pathways intact—markedly reduces the effectiveness of combined anti-PD-1 and anti-CTLA-4 treatment in a murine striatal tumor model.[83,86] The antitumor efficacy of combined PD-1 and CTLA-4 inhibition is augmented by VEGF-C overexpression in preclinical murine models. However, this enhancement is abolished upon inhibition of the CCL21/CCR7 pathway, demonstrating that VEGF-C's potentiation of immunotherapy is mediated through this signaling route.[87] Together, these findings not only confirm the functional role of cerebrospinal fluid-associated lymphatic vasculature as part of the conventional lymphatic system but also underscore the critical involvement of dorsal MLVs in brain tumor immunity, highlighting their potential as targets for immunotherapeutic strategies.

Brain region–mediated regulation of tumor immunity. Specific brain structures facilitate central nervous system dialogue with the immune system. These functionally distinct groups comprise: descending pathway regulators like the hypothalamus and brainstem; synchronizing regions such as the insular cortex; and predictive centers including the somatosensory cortex, amygdala, and hippocampus.[88] Beyond their roles in normal physiological processes, these brain regions participate in neuroimmune regulation that influences tumor development.

The hypothalamus serves as a central regulator of the endocrine system, integrating signals from other brain areas to control essential processes including hunger, thirst, body temperature, circadian rhythms, and sleep.[88] It regulates peripheral physiological functions primarily via two principal neuroendocrine axes: the hypothalamic-neurohypophyseal system and the hypothalamic-pituitary portal system. Certain regions of the hypothalamus directly sense blood-borne signals via specialized circumventricular organs, which possess fenestrated capillaries allowing hormone release into circulation.[89] Increased peripheral IL-6 in breast cancer can cross the blood-brain barrier to activate paraventricular hypothalamic CRH neurons. The resulting HPA axis stimulation induces glucocorticoid secretion and establishes a persistent stress state.[90] Persistent stress also leads to prefrontal glutamate neuron overactivation, increasing microglial IL-1β release and suppressing hippocampal neurogenesis, forming a positive feedback loop[91] that supports tumor progression. In preclinical breast cancer models, optogenetic stimulation of ventral tegmental area (VTA) dopaminergic projections to the medial prefrontal cortex was demonstrated to mitigate stress-promoted tumor growth and delay disease progression.[92–95] The anti-tumor effect of VTA activation extends to other malignancies, including melanoma and lung cancer, where it suppresses oncogenesis by modulating bone marrow sympathetic innervation and altering the function of MDSCs.[96] These findings provide preliminary insight into how neuromodulation may enhance antitumor immunotherapy.[15,97]

While the direct neural mechanisms governing peripheral tumor growth are still not fully understood, emerging evidence implicates the lateral septum (LS)[98]—a brain region integral to emotional processing, motivation, and affective states like reward and anxiety—in promoting cancer progression. In a colorectal cancer mouse model, a polysynaptic pathway from the LS to the lateral hypothalamus (LH) and sacral parasympathetic nucleus (SPN) connects via GABAergic neurons to intestinal cholinergic neurons, which project into the tumor microenvironment. This neural pathway increases the secretion of GABA from cholinergic neurons within the enteric nervous system. The released GABA then stimulates the epsilon subunit of the $GABA_A$ receptor present on cancer cells. This upregulates Tspan1 expression and promotes proliferation. Additionally, LS GABAergic neurons and intestinal GABA influence the tumor immune microenvironment by modulating infiltration of $CD68^+$ macrophages and $CD3^+$ T cells.[98]

The foregoing sections addressed neuro-tumor interactions within the uniquely enclosed central nervous system. By contrast, in solid tumors that are densely innervated by the peripheral nervous system — notably pancreatic, prostate, and gastric carcinomas — the nervous system is equally deeply integrated into the tumor microenvironment and fulfills a pivotal regulatory role, mediated through its two principal divisions (sensory and autonomic

nerves) via discrete anatomical substrates and molecular mechanisms.

OVERVIEW OF THE PERIPHERAL NERVOUS SYSTEM

PNS consists of all nerves located outside the CNS and is divided into sensory and autonomic components.[2] These nerves are capable of transmitting direct, real-time information to peripheral tissues. In solid tumors, this is evidenced by the tumor's ability to receive innervation from peripheral nerve fibers, which aids in the formation of the tumor microenvironment.

Tumor microenvironment

Hanahan and Weinberg proposed that tumors should no longer be viewed simply as masses of abnormally proliferating cells, but rather as new organs composed of multiple cell types and organ systems interacting through complex mechanisms.[99,100] In the development of malignant tumors, cancer cells proliferate uncontrollably, forming small tumor aggregates. In response to localized hypoxia, cancer cells within the tumor core trigger signaling pathways that promote the production and secretion of chemokines and growth factors, leading to a remodeling of the local microenvironment.[101] Diverse cellular populations—including immune, endothelial, and neuronal cells, respond to these oncogenic signals through their surface receptors, recruiting them to the tumor.[102,103] These cells, in turn, express a series of genes in response to the abnormal microenvironment, establishing a complex communication network within the tumor microenvironment.[104,105,106] The tripartite interaction between the tumor, nervous system, and immune cells makes an essential contribution to the establishment of an immunosuppressive tumor microenvironment.

As previously discussed, the nervous system plays a central role in regulating organ development, tissue homeostasis, and regeneration, and similarly,[14] it is crucial to the functioning of the tumor microenvironment. The nervous system is involved in the recruitment and regulation of immunosuppressive cells within this microenvironment. Tumor-associated macrophages (TAMs), Tregs, and MDSCs are the main immune cells that infiltrate tumors.[104] The release of growth factors such as catecholamines by tumor-associated sympathetic nerve fibers and adrenal glands, in addition to cytokines like IL-10, IL-4, and VEGF-A, collectively contributes to the polarization of M2 macrophages.[107] CCL2 and CXCL12 recruit M2 macrophages, Tregs, and MDSCs via the CCR2 and CXCR4 receptors, respectively.[108] Additionally, prostaglandin E2 (PGE2) stimulates MDSCs, preventing immune cell maturation and maintaining local immune suppression.[109] IL-6 impairs NK cell cytotoxicity through STAT3 pathway activation, leading to decreased surface expression of key activating receptors including NKp30 and NKG2D.[110] TGF-β initiate signaling cascades, to elevate the surface expression of CD73 and PD1 on both CD4+ and CD8+ T cells.[111] This leads to the functional suppression and polarization towards an exhausted phenotype in these T cells.

Tumor cells reprogram the functions of normal cells within the tumor microenvironment, thereby promoting tumor progression, metastasis, and malignancy.[112] Tumor-induced nerve damage, via myelin degradation, also contributes to the immunosuppressive environment of the tumor. After neuronal injury, the gene ATF3 mediates damage signaling within the neurons, leading to upregulation of type I interferon and IL-6 pathways. Tumor-associated nerve damage attracts immune cells to the perineural microenvironment, thereby promoting healing and nerve regeneration, a process primarily dominated by immunosuppressive macrophages.[113] As cancer advances, the burden of cancer-induced nerve injury (CINI) increases, resulting in greater tumor-associated nerve damage. This shift from acute to chronic inflammation contributes to the chronic infiltration of pro-healing, immunosuppressive cells into the perineural microenvironment, ultimately influencing the overall immune status within the tumor and impairing antitumor immunity and PD-1 blockade therapy efficacy.[114]

Numerous factors released by nerves and immune cells enhance angiogenesis within the tumor microenvironment. Norepinephrine, released by tumor-associated sympathetic fibers, acts on endothelial cells via the β2/3 signaling pathways, reducing oxidative phosphorylation and directly triggering angiogenesis.[115] In addition, the polarization of M2 macrophages to express and secrete VEGF indirectly facilitates tumor neovascularization.Tumor-associated macrophages release Sema4D, which binds to the Plexin-B1 receptor on endothelial cells, promoting angiogenesis and vascular maturation.[116] Moreover, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) can promote angiogenesis independently of VEGF.[117]

Moreover, neuro-supportive cells, including Schwann cells, enteric glial cells, and stromal cells, as well as the extracellular matrix, play an essential role in shaping the immunosuppressive tumor microenvironment.

Peripheral nervous system modulation of the tumor microenvironment and antitumor immunity (Figure 2)

Sensory nervous system: neuropeptide signaling from nociceptor neurons coordinates tumor growth and immunosuppression. The SNS functions as an alternative neural communication route linking the brain with the periphery, responding to various forms of sensory input, including thermal,[118] mechanical, and chemical stimuli,[119] as well as inflammation-related factors[120] and bacterial-derived molecules.[121,122] Sensory C fibers, also referred to as peptidergic neurons, represent the most thoroughly investigated population within the field of neuroimmune interactions. Through the relay of sensory input to the brain for peripheral immune modulation, the sensory nervous system mediates systemic effects, while it also generates local responses via direct neuropeptide secretion in tissues.[123]

Pain-sensing peripheral sensory neurons, termed nociceptors, are formed by either unmyelinated (C) or myelinated (aδ) fibers. Pain, as a hallmark feature of cancer, represents a nociceptive response to various stimuli. The presence of sensory neurons within numerous solid tumors has been associated with unfavorable clinical outcomes.[96,124,125] In addition to utilizing glutamate as their principal neurotransmitter, nociceptors employ neuropeptides like substance P (SP) and calcitonin gene-related peptide (CGRP) for essential communication with central and peripheral cells.[126,127] The sensitivity of nociceptor neurons can be heightened[128] by signals from cancer or immune cells, such as cytokines (e.g., IL-1β, TNF)[129] and immunoglobulins.[130] Driven by neuropeptide release (e.g., SP, CGRP), this hyperexcitable state orchestrates a spectrum of pro-tumorigenic effects, ranging from enhanced proliferation,[96] angiogenesis,[131] and metastasis to regulation of lymphatic antigen flow[132] and promotion of immune escape and exhaustion.

Glutamate: multifaceted functions as a nutrient factor and signaling molecule. As one of the most prevalent amino acids in the organism, glutamate serves as the primary neurotransmitter for nociceptors and participates crucially in nutritional, metabolic, and signaling pathways. Glutamate functions as a potential tumor progression promoter by providing both growth signals and metabolic energy in malignant cells,[133,134] while also holding promise as a diagnostic biomarker.

The conversion of glutamine to glutamate is mediated by glutaminase.[135] Elevated glutamine hydrolysis has been observed in numerous aggressive human cancers, such as colorectal cancer (CRC),[136] gliomas,[137] pancreatic cancer,[138] melanoma, and breast cancer, leading to increased glutamate expression.[126,127,129,135] In prostate cancer, reduced glutamate levels are associated with slower tumor growth, less invasion, and enhanced cancer cell apoptosis.[139] In breast cancer, glutaminase activity is markedly elevated, and the glutamate-to-glutamine ratio (GGR) is positively correlated with prolonged patient survival, representing a favorable prognostic factor.[133,135] The glutaminase inhibitor CB-839 demonstrated significant antitumor efficacy in patient-derived xenograft (PDX) models of ER^+/Luminal B breast cancer[140] suggesting that targeting glutamine metabolism constitutes a promising therapeutic strategy for multiple cancer types. In CRC, changes in glutamine metabolism are particularly pronounced. Elevated glutaminase (GLS) levels in CRC tumors correlate with not only decreased T-cell infiltration but also compromised cytotoxic activity. By blocking the metabolic flux of glutamate into glutathione (Glu-GSH), this intervention induces ROS-related signaling in tumor cells, which subsequently upregulates immunoproteasome activity and ultimately enhances tumor immunogenicity.[141] This discovery suggests that targeting the Glu-GSH metabolic pathway could provide a new approach for immunotherapy in colorectal cancer.

Both mGluRs and iGluRs glutamate receptors are distributed not only in the CNS but also in peripheral tissues (e.g., lung, breast, pancreas).[142–144] Elevated or aberrant expression of mGluRs has been detected in multiple cancer types. mGluR1 has been confirmed by numerous studies to interact with key intracellular pathways closely associated with melanoma, breast

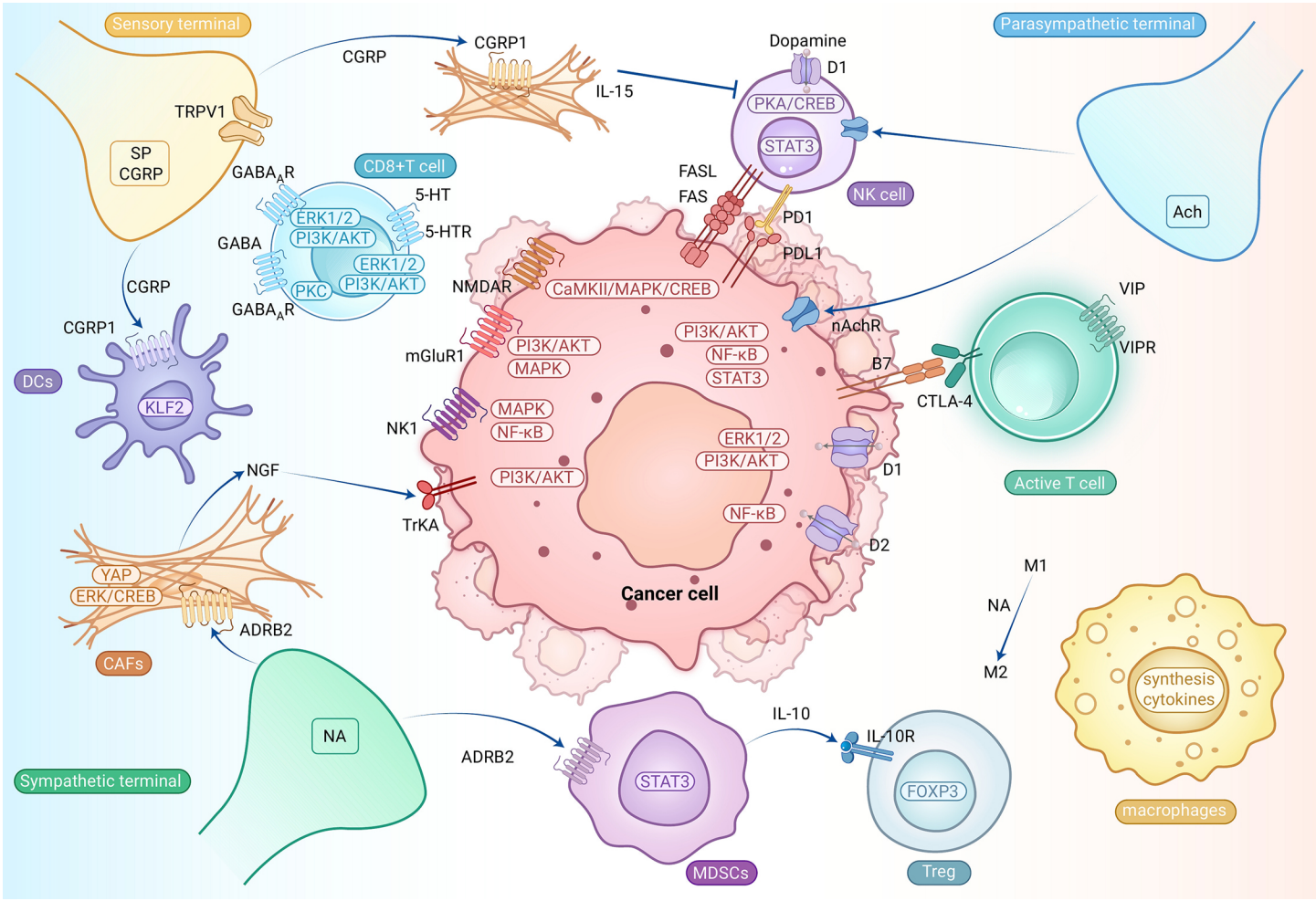

Figure 2. Regulation of the TME by the peripheral nervous system Parasympathetic nerve fibers release acetylcholine, which promotes the development of lung tumors via signaling pathways such as PI3K/AKT, NF-κB, and STAT. Norepinephrine induces cancer cell proliferation and the production of NGF, while also prompting the alternative (M2) activation of macrophages. Sympathetic stimulation can induce CAFs to secrete NGF, thereby increasing tumor innervation and promoting tumor progression. The role of the NMDAR is to activate MAPK and CaMK, which in turn activates the CREB transcription factor. Autonomic and sensory fibers release neurotransmitters and neuropeptides that modulate immune responses. CGRP activates RAMP1 in CAFs, inhibits the expression of IL-15, and suppresses the infiltration and cytotoxic function of NK cells. This positive feedback loop that promotes the progression of PDAC. Additionally, CGRP can influence DC development by activating cAMP-related pathways and elevating KLF2 levels.The expression of cell death receptors (such as FAS/PD-1) on T cells and cancer cells (e.g., PD-L1) is regulated by neurotransmitters, thereby altering tumor immunity within the TME.GABA receptors influence tumor growth through the MAPK and PI3K/Akt pathways, as well as the PKC-CREB axis. Dopamine modulates cancer cell behavior through D1-like and D2-like receptor pathways. DRD1 inhibits osteosarcoma cell growth via the ERK1/2 and PI3K/AKT pathways. The DRD1-cAMP-PKA-CREB signaling pathway in NK cells enhances their cytotoxicity and IFN-γ production. DRD2 suppresses breast cancer through the NF-κB signaling pathway.

cancer, and other tumors,[142] like the AKT and MAPK pathways. Its encoding gene, Grm1, has been verified to function as an oncogene in epithelial cells.[145] Glutamate is the primary agonist of N-methyl-D-aspartate receptor subtype 2B (NMDAR2B), and aberrant NMDAR2B methylation represents an important prognostic predictor for esophageal squamous cell carcinoma and non-small cell lung cancer. Genetic analyses demonstrate elevated methylation expression of NMDAR2B in tumor tissues relative to normal counterparts.[146,147] Additionally, NMDAR signaling mediated by GLUN2-B facilitates breast cancer metastasis to the brain, correlating with poor prognosis.[23] Recent studies on PDAC reveal significantly increased expression of NMDA receptor subunit GRIN2D, a key component of the NMDA receptor. Compared with CNS tumors such as glioma, both share the core pro-tumorigenic pathway centered on AMPA/NMDA receptors as signaling hubs and Ca^{2+} influx as the downstream effector. However, fundamental differences exist in the modes of neuro-tumor interaction: gliomas form bona fide synapses with intrinsic neurons, as validated electrophysiologically, and can actively remodel and prune surrounding synapses to optimize signal reception, yet signal transmission is predominantly unidirectional, In contrast, PDAC forms structurally distinct "pseudo-synapses" through glutamate-GRIN2D signaling and establishes a bidirectional feedback loop between the tumor and nerves — upon receiving neural signals, tumor cells secrete transforming growth factor-α (TGF-α), which binds EGFR on nerve surfaces to reciprocally stimulate nerve growth and branching, forming a closed-loop regulatory network of glutamate-GRIN2D signaling-tumor proliferation-TGF-α-nerve growth. Furthermore, PDAC uniquely couples glutamate signaling with KRAS-driven glutamine metabolic reprogramming, whereas glioma exhibits distinctive synaptic plasticity.[138] At the therapeutic level, these differences carry direct translational implications: glioma requires BBB-penetrating agents, whereas PDAC may benefit from non-BBB-penetrating GRIN2D-NMDAR inhibitors, offering a potentially wider therapeutic window with minimal CNS side effects.[148] Moreover, glutamate can influence PDAC progression by activating AMPARs. The KRAS mutation, a hallmark of PDAC, reprograms glutamine metabolism, and inhibition of this metabolic pathway suppresses PDAC growth both in vivo and in vitro.[138] Glutamate may act as a molecular switch, activating MAPK signaling pathways and enhancing K-ras activity, which potentiates K-ras-driven oncogenic signaling and promotes malignant progression in precancerous pancreatic tissues. Inhibition of AMPA receptors reduces cancer cell migration and invasion, inhibiting pancreatic tumor growth.[149] Additionally, glutamate activates GluR3 receptors, which promote CD147/EMMPRIN expression and enhance the secretion of matrix metalloproteinases (MMPs), such as MMP-9,[142] facilitating extracellular matrix degradation and aiding tumor invasion

Substance P: NK1R axis-mediated immunomodulation and tumor microenvironment-dependent effects. As a sensory neurotransmitter, SP

regulates the function of both innate and adaptive immune cells by multiple intracellular mechanisms, including the regulation of cytokine production.[150] For example, SP potentiates the killing capacity of NK cells through increasing the expression of key cytotoxic components (e.g., perforin, granzyme, and NCRs).[151] It also promotes phagocytosis in macrophages and neutrophils and contributes to regulating the maturation and migration of DCs.[150–152]

Substance P primarily binds to the NK1 receptor (NK1R),[153] which is encoded by the TACR1 gene. The NK1R/SP signaling axis is closely linked to pro-tumor pathways, as it triggers NF-κB activation, thereby stimulating cytokine production, upregulating TLRs, and increasing PD-1 levels. Consequently, this signaling pathway is crucial for modulating immune responses. Elevated SP levels are linked to melanoma,[154] breast cancer,[155] and glioma progression.[156] However, the effects of NK1R/SP antagonists vary among different tumor types, and their anti-tumor efficacy is influenced by the TME. Aprepitant, a selective NK1R antagonist, has shown substantial anti-tumor activity across various cancers, including lung cancer, HNSCC, breast cancer, and hepatocellular carcinoma, and is considered a promising cancer therapy.[125,157–159] However, in models of breast cancer metastatic to the brain (4TBM) and breast cancer metastatic to the liver (4TLM), Inhibition of NK1R demonstrated a significant anti-metastatic effect in inflammatory models featuring high levels of leukocyte-secreted IL-6 and TNF; conversely, NK1R inhibition increased the metastasis rate in less inflammatory models.[160] These studies demonstrate that the efficacy of NK1R antagonism is contingent upon the tumor's capacity to elicit inflammatory responses, underscoring the pivotal role of the tumor microenvironment in modulating therapeutic outcomes.[160]

CGRP: RAMP1-mediated CD8⁺ T cell exhaustion as a central pathway in immune evasion. Compared to SP, CGRP, a neuropeptide produced by nociceptive neurons has a more diverse impact on the immune system. It may play an inhibitory role by suppressing innate immune responses, thus limiting inflammation-induced tissue damage and providing host protection. Upon stimulation of the cAMP-protein kinase pathway, CGRP enhances the secretion of the IL-10 while blocking NF-κB activation,[161] and concurrently reduces monocyte recruitment while impairing the activity of macrophages and type 2 innate lymphoid cells (ILC2s), leading to suppressed antigen presentation by T cells. At the same time, CGRP also demonstrates pro-inflammatory activity by the recruitment of eosinophils to inflammatory loci and their mediation of T cell adhesion, both processes being regulated by β-integrins.[162]

The mechanism of CGRP action is mainly mediated through its receptor, which is a heterotrimeric complex consisting of three subunits: the calcitonin receptor-like receptor (CLR), receptor activity-modifying protein 1 (RAMP1)-essential for CLR function and belonging to the single-transmembrane RAMP family-and receptor component protein (RCP), which facilitates intracellular G-protein signaling. Across multiple tumor models, CGRP has been demonstrated to promote tumor immune evasion through modulation of the immune microenvironment. In melanoma models, nociceptive neurons mediate immunosuppression in tumors by driving the exhaustion of cytotoxic CD8+ T cells.[163] High levels of RAMP1+ CD8+ T cells are associated with superior patient outcomes, a finding supported by scRNA-seq.[125] Oral squamous cell carcinoma is densely innervated by nociceptive nerves. Compared to controls, CGRP knockout mice in a syngeneic oral cancer model exhibited enhanced presence of CD4+ and CD8+ T lymphocytes along with NK cells, accompanied by tumor reduction.[164] In the Lewis lung cancer mouse model, treatment with CGRP receptor antagonists[165] resulted in decreased tumor size and reduced angiogenesis. Either by blocking the release of neuropeptides from tumor-associated nociceptors or using antagonists to block RAMP1, the CGRP receptor,[165] can alleviate the exhaustion of tumor-infiltrating CD8+ T cells, suppress cancer growth, and extend overall survival.

In PDAC, the crosstalk between nociceptor neurons and cancer-associated fibroblasts (CAFs) constitutes a critical mechanism underlying tumor immune evasion. Nerve growth factor (NGF) secreted by CAFs promotes CGRP release from nociceptive neurons, which subsequently activates RAMP1 receptors in CAFs, suppresses IL-15 expression, and consequently inhibits NK cell tumor infiltration and cytotoxic function, establishing a positive feedback loop of NGF-CGRP-RAMP1-IL-15-NK cell dysfunction that drives PDAC progression and exacerbates cancer-associated pain. Thus, nociceptive neurons do not directly affect tumor cells, but instead "paralyze" NK cells via CAFs, revealing a tripartite interaction between neurons, stroma, and immune cells.[166] In GC, Timothy C. Wang's team used gastric cancer organoid-DRG 3D co-culture models, optogenetic activation of gastric tumor cell depolarization, and single-cell sequencing to show that nociceptive neurons, through NGF-dependent mechanisms, amplify in the gastric cancer microenvironment. By releasing CGRP, they activate RAMP1 receptors on tumor cells, driving calcium signaling and tumor proliferation.[167] Current FDA-approved medications targeting the RAMP1-CGRP pathway could potentially neutralize CGRP's immunomodulatory effects on CD8+ T cell cytotoxicity,[168] and the above findings provide a potential therapeutic strategy for targeting nerve-tumor interactions.

Furthermore, in medullary thyroid cancer (MTC), CGRP expression is linked to abnormal DC development, which impairs tumor-infiltrating T cell function. CGRP affects DC maturation through activation of cAMP-dependent signaling and increased KLF2 expression, thereby inhibiting T cell activation, CGRP receptor antagonists can reverse the aforementioned effects in vitro.[169] A cluster of RAMP1-positive B cells has been identified in esophageal squamous cell carcinoma that has developed resistance to neoadjuvant immunotherapy. These RAMP1+ B cells secrete immunoregulatory cytokines, weakening the killing capacity of CD8+ T cells and contributing to tumor escape. Combining RAMP1 inhibitors with anti-PD-1 therapy significantly enhanced anti-tumor immunity and slowed tumor progression in vitro. These findings demonstrate that targeting the CGRP-RAMP1 axis can reverse tumor immune evasion through multi-dimensional remodeling of B cell function, enhancement of effector T cell activity, and improvement of dendritic cell developmental status, providing a novel therapeutic strategy for overcoming immunotherapy resistance.[170] More broadly, DC maturation and antigen cross-presentation are central to productive T-cell antitumor immunity and immunotherapy responsiveness.[171]

TRPV channels: thermosensitiveion channels and cancer pain regulation. Various stimuli are known to stimulate ion channels at nociceptive nerve terminals, acting as molecular transducers that trigger neuronal depolarization and activate nociceptive transmission in pain pathways. Among the TRPV family, particularly TRPV1-4 (commonly referred to as thermosensitive TRP channels due to their responsiveness to heat) are integral to pain and inflammation processes. TRPV1, as the only receptor specifically activated by capsaicin, has shown therapeutic promise. This receptor is primarily expressed in neural tissues such as Aδ and C fibers, as well as in sensory neurons within the DRG, trigeminal ganglia, celiac ganglia, and jugular ganglia. Additionally, TRPV1 is found in various regions of the brain, functioning as a molecular component that integrates different forms of noxious stimuli. During inflammation, TRPV1 activity is upregulated, inducing calcium influx and the production of neuropeptides like SP and CGRP, which exacerbates the inflammatory response. A substantial body of evidence indicates that the prolonged activation or inactivation of this inflammatory pathway can significantly affect tumor growth and metastasis, positioning TRPV1 as a potential target for cancer pain management. Activation of TRPV1+ nociceptive neurons notably accelerates gastric cancer growth, facilitates ulcer healing, and promotes tumor proliferation.[167] In a PDAC mouse model, chemical ablation of TRPV1+ nociceptive neurons effectively protected the mice from tumor recurrence.[124] In another experiment with B16F10 melanoma cell-injected mice, genetic ablation of the TRPV1 lineage reduced the exhaustion of tumor-infiltrating white blood cells, suppressed tumor growth, and resulted in nearly a threefold increase in mouse survival.[163] While TRPV1 upregulation is documented in these malignancies, controversy persists regarding its functional activity within cancer cells. Although TRPV1-targeted pharmacological approaches have been investigated for their immunomodulatory potential, preclinical studies have yielded inconclusive outcomes.[172,173]

Vasoactive intestinal peptide (VIP): vasoactive intestinal peptide and tumor immunomodulation. VIP is mainly generated by nociceptive neurons of the vagus nerve. Additionally, sympathetic neurons contain varicosities that store neuropeptides, which are co-released with norepinephrine. Elevated plasma VIP levels have been detected in patients with PDAC, and its receptors are notably more abundant in activated T cells. Compounds that show affinity for VIP receptors, such as the experimental VIPR antagonists ANTO08 or ANT308, inhibit VIP-VIP receptor (VIPR) signaling.[174] This inhibi-

tion enhances anti-tumor immunity in PDAC models, especially when combined with anti-PD1 antibody therapy, indicating a promising potential for novel combination therapies.

Nociceptive neurons are critical to shaping both the cancer metabolic landscape and the TME. Integrating these findings with current immunomodulatory therapies in clinical oncology could help restore immune cell function, boost the effectiveness of immunotherapy, and overcome treatment resistance.

The autonomic nervous system (ANS) overview: antagonistic regulation of the SNS and PSNS. Comprising the sympathetic (SNS) and parasympathetic (PSNS) nervous systems, the ANS maintains homeostasis by regulating involuntary functions including blood pressure, heart rate, and gastrointestinal motility. These systems exert antagonistic effects on physiological processes: the SNS mediates "fight or flight" responses, while the PSNS supports "rest and digest" activities.[9] The SNS, whose principal neurotransmitter is norepinephrine, extensively innervates immune organs such as the spleen, bone marrow, lymph nodes, and thymus. Conversely, the PSNS primarily employs acetylcholine (ACh) as its neurotransmitter. Both systems modulate immune activity, and immune cells express receptors for ANS-derived neurotransmitters and neuropeptides.[175] Furthermore, immune cells can produce neuroactive factors, underscoring the bidirectional crosstalk between neural and immune systems.[176]

Sympathetic nervous system: catecholamine-mediated dual regulation of tumor biology. SNS is mainly divided into systemic and local components functionally and anatomically. It regulates the functions of nearly all organ systems in the human body through two ways: one is the localized release of neurotransmitters and catecholamines at sympathetic nerve terminals, and the other is the entry of these substances into the systemic circulation. Sympathetic fibers from the central nervous system reach the adrenal glands (especially the adrenal medulla), triggering chromaffin cells in the adrenal glands to secrete epinephrine and norepinephrine. These neurotransmitters gain access to the bloodstream directly, enabling their transport to all parts of the organism. Meanwhile, the sympathetic fibers in each tissue can be activated independently from those in other regions, resulting in the localized release of norepinephrine. The above mechanism extends specialized innervation throughout virtually all tissue systems, so the organism can achieve precise regulation of specific tissues through these descending neural innervations.

Adrenergic Signaling and its Implications for Cancer Therapy. Adrenergic agonists in vivo promote oncogenic signaling in cancer cells, whereas antagonists exert inhibitory effects on apoptosis evasion,[177] proliferation,[178] survival,[179] and invasion[180] via adrenergic receptor signaling pathway. The effects of adrenergic signaling extend to additional tumor microenvironment components like endothelial cells and immune cells. Norepinephrine preferentially binds to α-adrenergic receptors (ADR), such as α2-ADR (ADRA2), as well as β1-ADR (ADRB1), β2-ADR (ADRB2), and β3-ADR (ADRB3) (Table1.Adrenergic Receptors and Tumor Immune Regulation).[181–184] The findings highlight the crucial link between adrenergic signaling and anti-tumor immune responses, as well as the cancer-specific interactions between the adrenergic system and diverse immune cells.

An increasing amount of clinical evidence has established a link between stress and cancer prognosis.[185] Stress can be divided into acute and chronic types, each of which exerts different effects on tumor immunity. Acute stress boosts IgG1 and interferon levels via adrenergic receptor activation on CD4+ T and B cells, whereas chronic stress exerts a significant immunosuppressive effect on the immune system.[186,187] Epidemiological and genomic research indicates that chronic stress not only increases the number of macrophages in the TME, but also upregulates genes such as Tgfb, Arg1, Cox2, Mmp9, Vegf, and Vcam1, while reducing IFN-β gene expression. It promotes tumor growth through MDSCs, which accumulate in the TME and have an immunosuppressive action on both animal and human immune systems. β-AR antagonist treatment prevented metastasis in chronically stressed mice, but failed to exhibit this effect in non-stressed animals. This observation aligns with findings that stress modulates dendritic cell function, thereby influencing T lymphocyte function and the anti-tumor immune response in the TME. A preclinical investigation examined the T cell and DC populations in tumor-free and tumor-bearing mice under standard temperature (ST, 22°C; cold stress) and thermoneutral temperature (TT, 30°C; reduced stress levels). The results showed that under ST conditions, tumor-bearing mice had an increased number of CD11b+ myeloid cells, plasmacytoid dendritic cells, interferon, and immunosuppressive MDSCs compared to TT.[188,189] Moreover, chronic stress activates multisynaptic pathways in brain regions such as the lateral septum, hypothalamus (LH), and sacral parasympathetic nucleus (SPN). These pathways connect through GABAergic neurons to enteric cholinergic neurons, increasing GABA levels within the tumor and promoting tumor growth. Both LS GABA neurons and gut-derived GABA exert regulatory effects on the TME by affecting CD68+ macrophage and CD3+ T cell infiltration.[98]

Studies have recognized surgery as a crucial stressor,[190] which mediates the inhibition of NK cells. Cytotoxic T cells and NK cells appear to facilitate postoperative cancer metastasis and tumor cells spread.[191] Clinical studies have demonstrated significantly elevated MDSC levels in breast cancer patients experiencing high levels of psychological stress.[192] Increased postoperative stress suppresses immune surveillance function, which is associated with an elevated risk of cancer recurrence.[193] These findings were further corroborated in both the rat MADB106 mammary adenocarcinoma lung metastasis model and the murine B16F10.9 melanoma model.[190,194] In conclusion, adrenergic signaling-mediated stress responses influence tumor immunity by regulating the frequency and activity of regulatory immune cells, leading to negative effects on effector cell functions.

Building upon the evidence presented, adrenergic tumor innervation has been associated with lower survival rates, local lymph node spread, and a pro-metastatic phenotype in head and neck squamous cell carcinoma (HNSCC)[195] and prostate cancer.[115,196] β-blockers as a perioperative strategy has shown potential in sensitizing melanoma and lung tumors to immunotherapy,[197] and their combination with immunotherapy could emerge as a promising adjunctive treatment. It is speculated that immune checkpoint blockade resistance is mediated by adrenergic stress, resulting in the upregulation of checkpoint molecules like PD-1, FOXP3, and LAG3, which in turn induces T-cell exhaustion.[198] When combined with ICB in melanoma and drug-resistant pancreatic cancer mouse models, β-adrenergic receptor antagonists impair β1-adrenergic signaling, thereby amplifying reactivity of CD8+ T-cell and inducing differentiation of tissue-resident memory T-cell.[182]

However, unlike patients with other malignancies, colorectal cancer cases exhibited sympathetic nerve presence during early disease stages, correlating with improved prognosis and decreased lymph node metastasis.[199] Analysis of a colorectal cancer case-control cohort revealed no association between β-blocker administration after diagnosis and patient mortality.[200] These findings highlight the need for further studies to determine the optimal conditions for β-blocker effectiveness.

Parasympathetic nervous system: bidirectional regulation by the cholinergic system. As outlined, the SNS participates in the neurocoordination of immune cell trafficking and function. On the other hand, the parasympathetic nervous system, primarily via acetylcholine, serves as a key regulator of anti-inflammatory responses in peripheral immunity. While initial findings indicated that parasympathetic nerve activity could promote tumor metastasis,[150] more recent studies suggest that parasympathetic influence on tumor progression may differ across various cancer types, producing distinct effects on disease progression.

Contribution of Acetylcholine and Parasympathetic Nervous System to Immunoregulation in Cancer. Acetylcholine (ACh), the primary neurotransmitter of the PSNS, transmits signals through two principal receptor families: the nicotinic acetylcholine receptor (nAChR) and muscarinic acetylcholine receptor (mAChR) types. PSNS activation, typically enhanced by α7nAChR on splenic macrophages, boosts anti-cancer immune responses.[201,202] Action potentials trigger acetylcholine release in splenic memory CD4+ ChAT+ T cells, which acts on macrophage nAChRs to inhibit pro-inflammatory cytokine and HMGB1 release,[203] contributing to vagus nerve-mediated anti-inflammatory responses.[176,204] In a breast cancer mouse model, acupuncture was shown to enhance vagus nerve activity, resulting in reduced levels of pro-inflammatory cytokines (IL-1β and TNF-α), while significantly enhancing both the proportion and cytotoxic function of CD8+ T cells and NK cells, and suppressing the aggregation and immune-suppressive function of MDSCs.[205] Moreover, vagal nerve activation reduced the expression of PD-1 and PD-L1,

Table 1. Adrenergic receptors and tumor immune regulation.

Receptor Type	Effect	Cancer Type	Mechanism / Signaling Pathway
α2-ADR (ADRA2)-Direct Regulation of Tumor Cell Biology			
Anti-tumor			
ADRA2	Activation of anti-tumor immunity	Colorectal cancer	Macrophages activate T cells to mediate anti-tumor response[184]
ADRA2 agonist (monotherapy)	Potent anti-tumor activity	Multiple tumor types	Effective in human cancer cell xenograft + human lymphocyte reconstitution model; no anti-tumor effect in immunodeficient models[191]
Pro-tumor			
ADRA2 (direct)	Promotes cancer cell growth	Colorectal cancer	α2-ADR-mediated activation of Y-related proteins promotes cancer cell growth[327]
ADRA2 (indirect)	Promotes tumor innervation and progression	Colorectal cancer	Sympathetic nerve stimulation → CAF → NGF → PI3K/AKT pathway promotes cancer cell growth[327]
β1-ADR (ADRB1)-Maintains T Cell Exhaustion State			
ADRB1	Associated with T cell exhaustion	Multiple tumor types	ADRB1 gene upregulation in exhausted T cells; often distributed near sympathetic nerves
β2-ADR (ADRB2)-Suppresses Tumors via Immunosuppression, Metabolic Reprogramming Inhibition, and Angiogenesis Regulation			
ADRB2	Enhanced immunosuppression; inhibits T cell activation	Multiple tumor types	1. STAT3 phosphorylation involved in MDSCs immunosuppression-increased MDSCs in tumors 2. Inhibition of metabolic reprogramming→ decreased glucose uptake and glycolysis[328–330]
ADRB2/3	Promotes tumor growth and angiogenesis	Multiple tumor types	β2/3 receptor deficiency → delayed tumor growth; double KO → tumor growth and angiogenesis arrest (β2 signaling deficiency → COA6↑ → oxidative phosphorylation↑ → angiogenesis switch activation; NE promotes tumor angiogenesis via VEGF and polarized M2 macrophage secretion)[2,115]
β3-ADR (ADRB3)-Pro-tumor Effects			
ADRB3 antagonists (SR59230A, L-748337)	Enhanced anti-tumor immunity	Melanoma	Reduces Tregs and MDSCs, increases NK cell number and cytotoxicity, increases M1/M2 macrophage and N1 neutrophil ratios[331]
Denervation / Antagonist Effects			
Chemical denervation (6-OHDA), Surgical denervation	Inhibits tumorigenesis and progression	Prostate cancer, Lung cancer	Inhibits prostate tumorigenesis and lung cancer progression in HCC827 and H446 cells[107]
Celiac ganglionectomy / 6-OHDA	Inhibits proliferation and oxidative phosphorylation	PDAC	In PDX and KPC mouse models, denervation significantly reduces tumor weight; tumor cell and CAF proliferation↓; oxidative phosphorylation genes↓; inflammation-related genes↑
6-OHDA + ICI	Enhances immunotherapy efficacy	PDAC (immune 'cold' tumor)	Denervation enhances immune checkpoint inhibitor efficacy[332]
Non-selective β agonist (long-term)	Inhibits T cell activation, IFN-γ production, and cytotoxic killing; impairs immunotherapy response	B-cell lymphoma	Directly inhibits CD8+ T cell activation, IFNγ production, and cytotoxicity; promotes lymphoma development; impairs CD8+ T cell response to anti-PD-1 and anti-4-1BB[201]

resulting in reduced tumor growth and distant metastasis in breast cancer.[6] In a colorectal cancer model, electrical stimulation of the vagus nerve induced cholinergic activation, prompting trefoil factor 2 (TFF2) secretion by splenic memory T cells. In TFF2-deficient mice, Increased PD-L1+ MDSCs suppressed IFN-γ secretion and CD4+ T cell proliferation, thereby restraining tumor growth via MDSC blockade.[206] Consequently, transgenic overexpression of TFF2 and viral vector-mediated TFF2 transfection are promising potential therapeutic approaches .

The vagus nerve acts as a key regulator of parasympathetic control in subdiaphragmatic viscera, directly or indirectly influencing tumor initiation and cancer stem cells, leading to diverse outcomes in various cancer types. Vagotomy, which results in cholinergic nerve deprivation, increases tumor invasiveness by promoting the producrion of cytokines such as TNF-α through an increase in macrophage numbers in the tumor microenvironment, ultimately reducing survival rates. This process has been shown to accelerate the development of pancreatic and gastric tumors.[207,208] Researchers found that after parasympathetic denervation, the expression of muscarinic acetylcholine receptor M1 (CHRM1) in pancreatic tumor epithelial cells decreased, stimulating cancer progression through the activation of EGFR/MAPK and PI3K/AKT signaling pathways. Postoperative treatment with epigallocatechin gallate (EGCG) decreased tumorigenesis with downregulated CD44 expression.[208] In contrast, the role of acetylcholine in gastric cancer follows a different mechanism. Muscarinic receptor subtype 3 (CHRM3) is overexpressed in gastric tissues, and it stimulates tumor progression by two pathways: first, by triggering EGFR signaling to enhance proliferation,[209] and second, by promoting the movement of tumor cells to facilitate metastasis. Additionally, CHRM3 regulates tissue stem cell function, supporting epithelial regeneration and potentially contributing to tumor initiation.[210,211] CHRM3 also activates YAP in the Hippo signaling, and activated YAP promotes gastric cancer development through Wnt signaling. This highlights the CHRM3-YAP axis as a potential treatment target for treating vagus nerve acetylcholine-dependent gastric cancer. Cluster cells expressing Dclk1 in the gastrointestinal tract increase local ACh levels through the expression of choline acetyltransferase (ChAT), but the precise carcinogenic pathway

remains unclear.[126] In CRC, the ACh-CHRM3 axis also contributes to tumor progression.

Contradictory findings and mechanistic complexity. Notably, the effects of parasympathetic nerves on tumors exhibit pronounced tumor-type dependence, with underlying mechanisms displaying markedly divergent effects across different cancers. This discrepancy may be attributed to the following factors: Regional variations in neural innervation density and functional compartmentalization: The vagus nerve primarily innervates the upper gastrointestinal tract (stomach, pancreas), where its anti-inflammatory effects predominate in upper gastrointestinal cancers. In contrast, the enteric neural plexuses of the colon are predominantly extrinsic sensory afferents,[199] suggesting that parasympathetic pro-tumorigenic effects may be more pronounced in colorectal malignancies. Subtype distribution of cholinergic receptors: ACh exerts diverse effects through muscarinic receptors (e.g., CHRM1, CHRM3) and nicotinic receptors (e.g., α7, α9). In pancreatic cancer, CHRM1 activation inhibits the EGFR/MAPK pathway (protective effect), whereas in gastric cancer, CHRM3 overexpression promotes EGFR signaling cascades and YAP activation (pro-tumorigenic effect).

Tumor immune contexture: The anti-inflammatory effects of the vagus nerve (mediated via α7nAChR-dependent macrophage inhibition) may be beneficial in immunologically "hot" tumors but may complicate immune surveillance in immunologically "cold" tumors such as PDAC. In genetically engineered mouse models of pancreatic cancer, concurrent use of acetylcholinesterase inhibitors showed no significant association with overall survival.[212] Similarly, acetylcholinesterase expression levels in tumor tissues of pancreatic cancer patients demonstrated no prognostic significance regarding survival outcomes. Methodological considerations: Importantly, the vagus nerve comprises a dual neural architecture, containing both parasympathetic motor fibers and sensory afferents,[9] which complicates the interpretation of independent contributions in experimental settings and may constitute a methodological factor underlying the contradictory findings.

In summary, the effects of the parasympathetic-cholinergic system on tumor biology exhibit high context-dependency. The development of therapeutic strategies targeting this pathway necessitates individualized assessment with careful consideration of tumor type, stage, and microenvironmental characteristics. Future investigations should focus on elucidating the precise roles of distinct cholinergic receptor subtypes within specific tumor contexts and developing more targeted therapeutic agents with enhanced specificity.

Neurotransmitters: cross-system signaling connecting the nervous, immune systems, and tumor microenvironment. Neurotransmitters, traditionally regarded as exclusive mediators of the central nervous system—such as GABA, serotonin (5-hydroxytryptamine, 5-HT), and dopamine—have now been firmly established as critical signaling molecules in regulating peripheral tumorigenesis and progression. Beyond their direct effects on tumor cells, these neurotransmitters profoundly influence tumor progression by shaping an immunosuppressive microenvironment.[213,214] GABA exhibits complex roles in tumor biology. Pro-tumorigenic signaling is primarily mediated through $GABA_A$ receptors (e.g., stimulating proliferation in prostate and breast cancers), whereas $GABA_B$ receptor activation may suppress the growth of certain tumors.[215–222] More importantly, GABA serves as a potent immunomodulator: in colorectal cancer models, GABA produced by B cells or plasma cells directly inhibits $CD8^+$ T cell function via $GABA_A$ receptors on their surface and recruits IL-10-secreting immunosuppressive macrophages, collectively suppressing antitumor immunity.[213,216,222–230] 5-HT predominantly stored and released by platelets, upregulates PD-L1 expression in tumor cells through a distinctive epigenetic mechanism termed "histone serotonylation," thereby facilitating tumor immune evasion from $CD8^+$ T cell attack. This finding unveils a direct link among platelet activation, neurotransmitter release, and immune checkpoint pathways.[231] Dopamine demonstrates multifaceted antitumor potential. It can directly inhibit tumor cell proliferation and angiogenesis through D2-like receptors while positively regulating the immune system.[232–235] For instance, sciatic nerve stimulation enhances NK cell cytotoxicity and IFN-γproduction via activation of D1-like dopamine receptor signaling on NK cells, offering a novel approach for activating innate immunity against tumors such as triple-negative breast cancer.[236] Targeting these neurotransmitter pathways has shown promising clinical translational potential.

Collectively, GABA, serotonin, and dopamine function as "cross-system" messengers, constituting the core language of neuro-immune-tumor crosstalk. Interventions targeting these neurotransmitter pathways hold promise for simultaneously modulating tumor cell behavior and the immune microenvironment, thereby opening novel avenues for cancer therapy.

Tumor hijacking of nerves

Emerging evidence reveals a reciprocal relationship: while the nervous system can regulate cancer progression, cancer remodels and hijacks the nervous system's architecture and function.[7]

Growing evidence indicates that tumors hijack nerves to replay developmental programs of organogenesis.[237] This is mediated through tumor-derived signals including growth factors, axon guidance molecules, and genetic material, which induce axonogenesis, neurogenesis, and neural reprogramming. These events collectively propel peripheral nervous system remodeling and institute a feed-forward circuit that supports cancer progression. Tumor cells also indirectly affect nerves through interactions with nerve-supporting cells and fibroblasts in the tumor microenvironment. Furthermore, the characteristic stressful conditions of the tumor microenvironment, such as hyperglycemia and acidity, also influence its innervation (Figure 3).[238]

Tumor-induced neurostructural remodeling: tumors promote axonogenesis in the tumor microenvironment by secreting tumor-derived factors. The TME contains abundant neurotrophic factors (such as NGF, BDNF, NT3, etc.), which stimulate nerve growth via their Trk receptors.[104,128] Intraneural macrophages activated by tumors exhibit increased secretion of GDNF, which induces cancer cell perineural invasion via the GFRα1 coreceptor and RET.[239–241]

Axon guidance molecules also promote axonogenesis in the tumor microenvironment. For instance, cancer cells drive the expression of Semaphorin 4F, promoting axonogenesis and regulating the differentiation process of neuronal precursor cells within the tumor microenvironment, thereby increasing intratumoral nerve density and cancer aggressiveness.[242–244] The axon guidance molecule netrin-1 acts as an oncogene in various cancer types and promotes the migration of gastric cancer cells along sensory dorsal root ganglion cells and perineural invasion of the sciatic nerve in vitro.[245]

Axon guidance molecules and genetic material encapsulated within exosomes contribute significantly to axonogenesis.[246] In a human papillomavirus (HPV+)-induced head and neck squamous cell carcinoma (HNSCC) model, EphrinB1 is incorporated into secreted exosomes. These EphrinB1-carrying exosomes facilitate axonogenesis in PC12 cells under in vitro and enhance tumor growth in vivo.[246] Notably, these exosomes lack NGF and BDNF, suggesting that tumor innervation can occur independently of classical neurotrophic factors. Furthermore, in HNSCC, exosomal contents such as miR-21-5p and miR-324 have been found to stimulate axonal growth and neurite extension within an in vitro trigeminal nerve model.[195,247] The tumor suppressor PTEN is one validated target of miR-21 while neuronal PTEN overexpression impedes neuronal development and neuritogenesis by suppressing the PI3K/AKT pathway.[248]

Cytokines and chemokines are important signaling molecules. Although they are not directly or significantly involved in neural remodeling, they can trigger changes in cancer cell secretions, thereby promoting remodeling of the peripheral nerves. For example, tumor-associated nerves induce cancer cell migration and perineural invasion via the CCL2-CCR2 and CXCL12-CXCR4 signaling pathways, and increase tumor cell expression of nerve growth factors, thereby promoting enhanced innervation within the tumor space.[249,250] Additionally, nerve-resident macrophages, by tracking CCL2 and CSF-1 gradients, accumulate in nerves invaded by tumor cells, further promoting perineural invasion.[239]

Tumors form functional synaptic connections with neurons. As mentioned earlier, within the central nervous system, direct synaptic connections exist between neurons and glioma cells, which can promote tumor proliferation and invasion.[17,18,251] Furthermore, metastatic breast cancer cells can utilize glutamate spilled over from neuronal synaptic clefts to accelerate tumor progression.[23] However, true synaptic structures had not been identified between cancers originating outside the central nervous system and

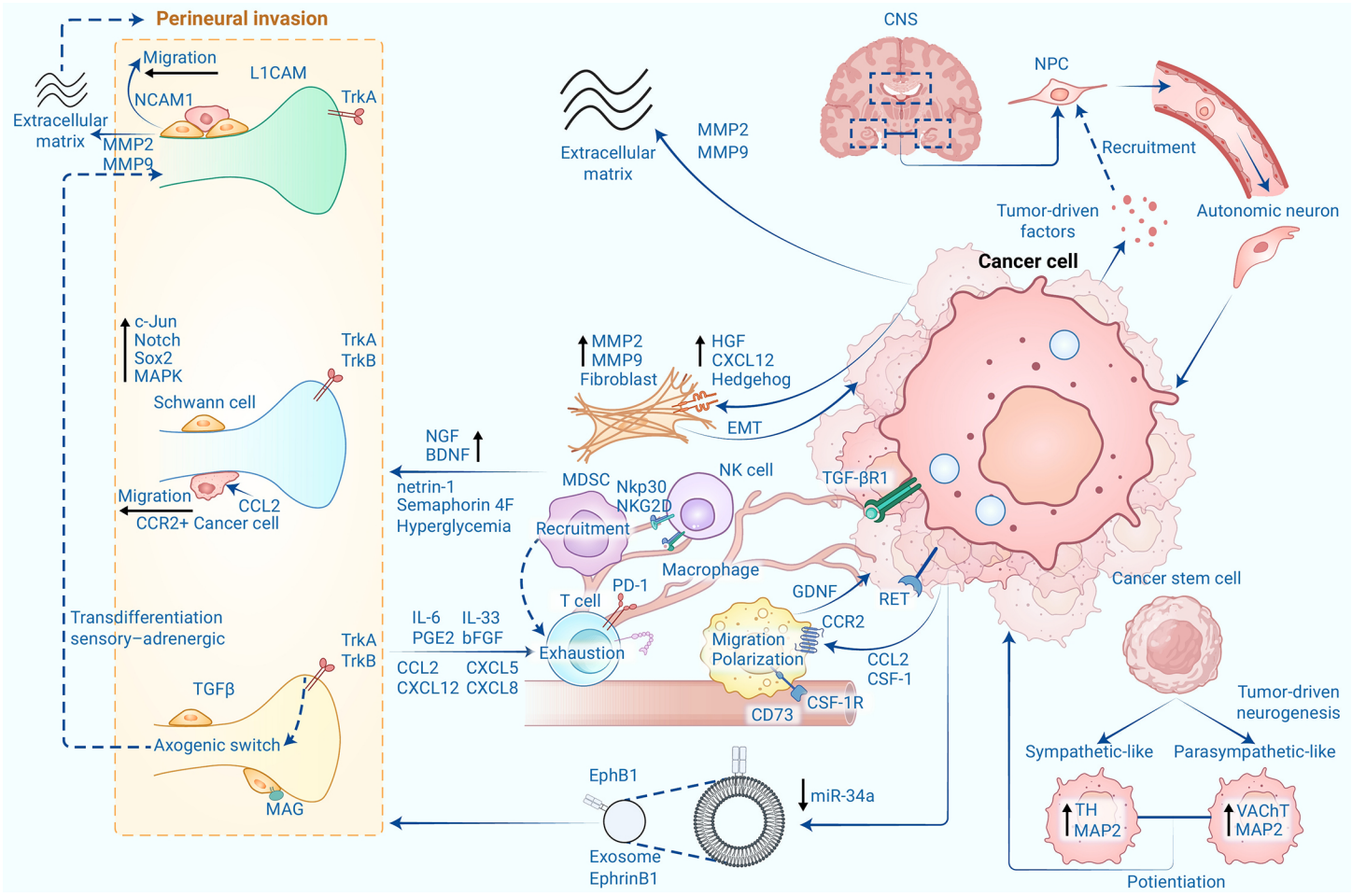

Figure 3. Cancer cells hijack nerves, neuronal support cells, immune cells, and stromal cells to promote tumor progression Different mediators released by autonomic nerves and sensory fibers regulate tumor initiation, progression, and metastasis. Meanwhile, cancer cells secrete NGF and BDNF to stimulate nerve growth via Trk receptors, and release axon guidance factors (such as Semaphorin 4F and netrin-1) to promote axonogenesis. Tumor cells also release exosome-encapsulated axon guidance factors and genetic materials that facilitate axonogenesis and neural reprogramming. Cancer stem cells express MAP2 and VAChT/TH, enabling them to differentiate into autonomic nerves. NPCs from the SVZ of the CNS can be attracted by tumor-derived factors, migrate through the bloodstream, infiltrate and colonize tumors, and differentiate into functional autonomic neurons that stimulate tumor growth. Cancer cells secrete CCL2 and CSF-1 to recruit endometrial macrophages and stimulate macrophage migration and polarization. SCs bind to tumor cells via adhesion molecules such as MAG, NCAM1, and L1CAM, recruiting them to nerves. CCL2 secreted by SCs promotes the migration of CCR2+ cancer cells along nerves. A positive feedback loop between SCs and macrophages mediated by bFGF/IL-33 facilitates macrophage polarization. Schwann cells express molecules such as TGF-β, PGE2, and IL-6, which are associated with NK cell dysfunction. They also upregulate CD73 and PD1 expression on CD4+ and CD8+ T cells, contributing to T cell exhaustion. Additionally, Schwann cells chemoattract MDSCs. Cancer cells express Hedgehog ligands and activate fibroblasts in a paracrine manner via the Sonic Hedgehog (SHH) signaling pathway. Activated fibroblasts upregulate the secretion of NGF, MMP-2, MMP-9, and HGF, thereby promoting tumor development and metastasis.

neurons.

Sakthivelu's research demonstrated that in a co-culture system of small cell lung cancer (SCLC) cells and cortical neurons, immunostaining targeting glutamatergic vesicles (anti-VGluT1 antibody) and the postsynaptic protein HOMER1 revealed colocalized structures at the interface between neurons and cancer cells. Further, electron tomography and 3D reconstruction of DsRed- or tdTomato-positive small cell lung cancer cells confirmed the presence of vesicle-filled synaptic boutons contacting the cancer cell plasma membrane. The researchers found that small cell lung cancer cells can form functional synapses with glutamatergic/GABAergic neurons in vivo, collectively mediating a tumor proliferation advantage through electrical activity and paracrine mechanisms.[24] In addition, in a study by Demir's team on PDAC and sensory neurons, transmission electron microscopy showed that presynaptic boutons in sensory neurons contained large dense-core vesicles (likely storing neuropeptides) and small synaptic vesicles (suggesting neurotransmitters like glutamate), apposed to electron-dense postsynaptic densities on PDAC cells. Further research suggested the formation of a functional pseudo-synapse between them, mediated by glutamate-induced activation of GRIN2D-containing NMDA receptors, promoting tumor growth and dissemination.[148]

Tumor-mediated neurogenesis. Cancer development relies on axonogenesis and nerve fiber outgrowth. In some tumors, the number of neurons per ganglion increases, indicating a potential neurogenesis process. However, the origin of these nerves has not been fully elucidated.

Tumors recruit CNS-derived progenitor cells to drive intratumoral neurogenesis. During cancer development, the subventricular zone may be hijacked to provide neural progenitor cells, thereby initiating neurogenesis during tumor formation. Magnon's research showed that CNS-derived doublecortin-expressing neural progenitor cells may penetrate the blood-brain barrier via porous vasculature, emigrate from the subventricular zone, be attracted by tumor-derived factors, migrate via the bloodstream, selectively infiltrate, and colonize prostate tumors and metastases, subsequently differentiating into functional active autonomic neurons which drive tumor progression.[196] However, it remains unclear which specific tumor-derived factors promote neural progenitor cell migration. Therefore, it is necessary to deeply Identify and define the tumor-derived factors that orchestrate the migration and differentiation of neural progenitor cells.

Cancer Stem Cells and Neuron-like Macrophages drive intratumoral neurogenesis. In peripheral tumors, neuron-like cells have been observed. For example, in gastric and colorectal cancers, stem cells differentiate into autonomic neurons expressing VAChT (a parasympathetic neuron marker) or TH (tyrosine hydroxylase, a sympathetic neuron characteristic). These cells also express MAP2,[252] which is found only in cancer stem cells within the tumor that possess neural differentiation potential. MAP2 knockdown in human

gastric and colorectal cancer stem cells decreased their neurogenic potential and inhibited the growth of patient-derived xenograft tumors, suggesting that these cells can differentiate into functional autonomic neurons to fuel tumor progression. In a parallel phenomenon observed in glioblastoma, tumor stem cells demonstrate the ability to undergo endothelial differentiation, which then construct vascular structures that nourish the tumor.[253-255] Inhibiting the differentiation of cancer stem cells into tumor-promoting phenotypes resembling neurons or endothelial cells holds promise as a viable approach for cancer treatment, but the key lies in identifying the factors and conditions that contribute to the transdifferentiation of cancer stem cell.

Furthermore, a recent study, through the mechanism of macrophage-to-neuron-like cell transition, identified a subset of tumor-associated macrophages with a neuron-like phenotype. These Tubb3+ macrophages exhibit loss of macrophage marker expression and expression of neurogenesis-related genes at the transcript level, potentially driving tumor neo-neurogenesis.[256]

Tumor-mediated neural functional reprogramming. Tumor cells achieve neural reprogramming via extracellular vesicles, converting sensory nerves into adrenergic nerves. Amit and his team first reported that oral squamous cell carcinoma with p53 deletion reprograms nerve fibers in the TME through EVs.[195] miR-34a, an inhibitor of neuritogenesis, shows reduced expression following the loss of tumor suppressor p53 function. EVs released from p53-deficient cells contain significantly lower levels of p53-regulated miR-34a miRNA, which not only promotes neurite outgrowth in sensory nerves but also induces neural reprogramming, transforming sensory nerves into adrenergic nerves.

Tumor Cells Enhance Neuronal Mitochondrial Function and Acquire Mitochondria from Neurons to Boost Metabolic Plasticity and Metastatic Potential. As previously discussed, cancer-induced differentiation of neuronal progenitor cells is a core component of neuron-cancer interactions established during cancer innervation.[257,258] Grelet's study demonstrated that in co-culture experiments involving aggressive mouse breast cancer cells (4T1) and neural stem cells (NSCs) derived from the mouse subventricular zone (SVZ), cancer enhances neuronal mitochondrial function. SVZ-NSCs exposed to 4T1 cancer cells exhibited a significant increase in mitochondrial mass, with mtDNA copy number per neuron rising from approximately 16 to 226. Furthermore, experiments using genetic modification and fluorescence-based techniques revealed that cancer cells acquire neuronal mitochondria via tunneling nanotubes. Recipient cancer cells displayed increased tolerance to oxidative and shear stresses, greater metabolic plasticity, and better redox balance. Additional experiments indicated that cancer cells acquiring mitochondria exhibited significantly higher metastatic potential. However, further research is needed to elucidate how tumors hijack neural components to gain metabolic support.[259]

Tumors indirectly affect nerves through nicroenvironment-supporting cells: Schwann cells. In the PNS, Schwann cells (SCs) are the predominant glial cell type.[260] They play roles in wrapping nerve fibers, producing myelin, providing nutritional support to neurons, constructing the neural extracellular matrix, maintaining neuronal survival, participating in the organization of perineuronal tissues, and regulating neuromuscular synaptic activity.[261–263]

Tumor-reprogrammed schwann cells. SCs are highly plastic and undergo cellular reprogramming in nerve injury and various cancers.[264,265] Quiescent myelinating Schwann cells and Remak Schwann cells are reprogrammed into non-myelinating repair Schwann cells, with upregulated expression of c-Jun, Notch, Sox2, and MAPK signaling pathways.[266,267] These reprogrammed cells demonstrate dynamic motility, release neurotrophic and chemokine signals, orchestrate immune cell recruitment, and ultimately remodel into specialized Büngner bands that direct the regeneration of damaged axons.[268]

The specific mechanism of SCs reprogramming in the TME remains unclear. Tumor-induced neural damage in adjacent tissues is a potential mechanism.[112] Multiple studies indicate this process is mediated by factors secreted by tumor cells.[269] In colon cancer research, scientists found that cancer cell-derived exosomal miR-21-5p can stimulate the secretion of NGF to promote SCs' proliferation and migration. Additionally, tumor-associated immune cells can also enhance SC reprogramming. Specifically in PDAC, the activation of the PI3K/Akt/c-myc pathway by macrophage-derived basic fibroblast growth factor (bFGF) elevates GFAP expression in SCs, thus promoting their transdifferentiation.[270] By reprogramming Schwann cells, tumors can hijack their normal physiological functions to promote tumor development, metastasis, and immune evasion.[271–273]

Schwann cells directly contact tumor cells to promote cancer cell migration and perineural invasion. Schwann cells bind to tumor cells via adhesion molecules myelin-associated glycoprotein (MAG), neural cell adhesion molecule 1 (NCAM1), and L1 cell adhesion molecule (L1CAM), recruiting them to nerves and promoting PNI.[262,274,275] SCs directly contact cancer cells through expressed NCAM1 and induce the formation of cancer cell protrusions. Subsequently, SCs insert themselves between cancer cells to disperse them, thereby promoting cancer cell migration and facilitating PNI. Secreted L1CAM can also act as a chemoattractant for tumor cells, enhancing tumor migration in a non-contact manner.

Tracks organized by non-myelinating SCs provide migration pathways for cancer cells. During this process, SCs exert forces on cancer cells to enhance their migration and invasion capabilities. Such Schwann cells establish tumor-activated Schwann cell tracks (TAST) that augment tumor cell motility, facilitate their migration, and induce epithelial-mesenchymal transition (EMT).[276]

Schwann cells secrete factors that promote cancer cell migration and perineural invasion through the tumor microenvironment. Reprogrammed Schwann cells also induce cancer cell invasion, epithelial-mesenchymal transition, and metastasis through the secretion of various molecules. SCs secrete neurotrophic factors (such as NGF, BDNF, NT3), chemokines (such as TNFα), and cytokines (such as CCL2), which collectively promote cancer growth. SCs co-cultured with colon cancer cells promote colon cancer cell proliferation and migration by releasing NGF, while colon cancer cell-secreted exosomal miR-21-5p enhances NGF expression in SCs via the VHL/HIF-1α pathway, thereby accelerating colon cancer progression.[270] This bidirectional feedback loop ultimately promotes colon cancer cell proliferation and migration. Co-cultivation with CRC cells triggers NF-κB-dependent IL-8 secretion from SCs, potentiating CRC cell migration and invasion. SC-derived CXCL5 and CCL2 induce a mesenchymal/migratory phenotype in tumor cells. TGF-β is a key inducer of EMT in tumor cells, primarily through the SMAD2 pathway;[277,278] IL-6 induces a similar effect through the STAT3 pathway.[279] Complementing these, other effectors like cathepsin D, PAI-1, and Gal-1 also enhance tumor cell motility.[280] Concurrently, SC-derived matrix metalloproteinases (MMP2, MMP9, MMP12) facilitate invasion by degrading ECM components.[281]

The tripartite crosstalk among SCs, macrophages, and cancer cells collectively drives tumor proliferation, PNI, and the onset of malignancy-associated pain. The core mechanism of this process involves SCs inducing macrophage polarization towards the pro-tumor M2 phenotype. SCs strategically secrete cytokines and chemokines such as CCL2, CXCL5, CXCL12, and CXCL8 to drive macrophage polarization, thereby promoting cell proliferation.[282–284] In specific tumor types, such as lung cancer, studies report that Schwann cells facilitate the homing of inflammatory monocytes from the bloodstream to the perineurium via secretion of CCL2 and activation of the CCL2-CCR2 signaling pathway, promoting their differentiation into macrophages. These macrophages subsequently produce cathepsin B, disrupting perineurium integrity and facilitating tumor invasion along nerves. Recent advances reveal a positive feedback loop between Schwann cells and macrophages. tumor-associated macrophages trigger Schwann cell activation through the bFGF/PI3K/Akt/c-myc/GFAP signaling axis, and in response, the activated Schwann cells release IL-33, which facilitates macrophage recruitment to the perineurium and promotes their M2 polarization. This loop accelerates cancer cell invasion along neural tracts.

SCs reprogrammed by melanoma exhibit the capacity to recruit MDSCs and potentiate their suppression of T-cell proliferation in vitro, suggesting a role for tumor-activated SCs in enhancing MDSC immunosuppressive function. Further research found that the overexpression of MAG, a type I transmembrane glycoprotein known to inhibit axonal regeneration in tumor-activated SCs, is a key factor contributing to this process.[281] In T-cell suppression assays, both MAG-overexpressing, melanoma-activated SCs and recombinant MAG protein independently augmented the immunosuppressive activity of MDSCs. Collectively, these findings demonstrate that SCs actively contribute to the recruitment and functional potentiation of MDSCs within the tumor microenvironment, thereby fostering an immunosuppres-

sive and tolerogenic landscape conducive to tumor immune evasion.

Therapeutic potential of targeting schwann cells. Reprogrammed Schwann cells within the tumor microenvironment actively contribute to cancer progression and exhibit pronounced immunosuppressive functions. Consequently, therapeutic strategies aimed at suppressing their phenotypic alteration or selectively depleting these cells hold considerable promise.[270,285,286]

Research indicates that the transcription factor c-Jun serves as a central regulator driving the transformation of Schwann cells into a cancer-associated state. These reprogrammed cells enhance the migratory and invasive properties of pancreatic cancer cells. In vivo studies show that the JNK inhibitor SP600125 modulates c-Jun activity and effectively reduces perineural invasion, suggesting a potential targeted approach for pancreatic cancer treatment.[276]

In genetically engineered mouse models of PDAC, localized injection of an adeno-associated virus expressing diphtheria toxin A under the GFAP promoter enables specific ablation of Schwann cells, leading to suppressed tumor initiation. Furthermore, in vivo administration of the small molecule fluorocitrate to eliminate Schwann cells not only curbs tumor growth but also promotes the infiltration and cytotoxic function of $CD8^+$ T cells, thereby increasing the responsiveness of pancreatic ductal adenocarcinoma to immunotherapy. Work by R.L. Bakst and colleagues has further demonstrated that radiation-induced Schwann cell death represents a key mechanism in mitigating perineural invasion, supporting the use of localized low-dose radiotherapy to nerves adjacent to tumors.[287] Nevertheless, minimizing collateral damage to normal neural function remains a critical challenge for the clinical translation of such approaches.

Enteric glial cells. The gastrointestinal tract is extensively innervated, particularly characterized by intrinsic innervation. The enteric nervous system (ENS) governs gut functions locally and operates autonomously from the central nervous system.[288]

Within the intestinal environment resides a substantial glial population. This includes Schwann cells, which ensheath peripheral neuron axons, and enteric glial cells that are intimately linked to the intrinsic neural network. These enteric glial cells are pivotal for preserving the integrity of the intestinal barrier, modulating immune activity, and facilitating repair and regeneration processes.

Furthermore, research indicates that the L1CAM and N-cadherin pathways mediate the adhesion and migration of colorectal cancer cells along enteric neurons.[289] Notably, Vallés and his team identified the activation of EGCs by tumor epithelial cells (TECs), tumor-infiltrating monocytes, and macrophages via IL-1, acquiring a pro-tumor phenotypic transformation. The transformed EGCs promote tumorigenesis, facilitating colon CSC expansion and CSC-driven tumorigenesis through a PGE2/EP4/EGFR-dependent pathway.[290,291]

Fibroblasts. Fibroblasts constitute a heterogeneous population of resident cells in numerous normal tissues, primarily responsible for producing the essential extracellular matrix components that ensure connective tissue integrity.[292] They are further implicated in pivotal processes such as wound healing, aging, and carcinogenesis. A key event in cancer development is the cancer cell-induced activation and subsequent conversion of these fibroblasts into CAFs, which are defined by their expression of alpha-smooth muscle actin (α-SMA).

In this activation process, cancer cells express Hedgehog ligands, paracrinally activating fibroblasts through Sonic Hedgehog (SHH) signaling.[293] Additionally, evidence suggests that in various cancers like pancreatic cancer or melanoma, cancer cells activate fibroblasts via exosomal miRNA.[294,295] CAFs can arise from multiple sources, such as differentiated bone marrow mesenchymal stem cells, EMT-driven transdifferentiated epithelial cells, and activated quiescent stellate cells.[296]

Beyond the above mechanisms, recent studies show that tumors can activate fibroblasts via MIRO2-mediated mitochondrial transfer from cancer cells to fibroblasts. Cancer cells transfer mitochondria to fibroblasts, thereby inducing pro-tumorigenic cancer-associated fibroblast characteristics. The transfer of functional mitochondria from cancer cells drives a series of changes in fibroblasts, including metabolic reprogramming, the upregulation of CAF markers, and the consequent secretion of pro-tumorigenic matrisome and secretome components.[297]

PDAC are notable for extensive desmoplasia, in which the extracellular matrix may represent up to 90% of the tissue. The close association between neural invasion and CAF-mediated fibrosis suggests a tripartite interaction among nerves, cancer cells, and CAFs.[298] Tumor-activated stellate cells, by upregulating the secretion of NGF, MMP-2, and MMP-9, not only assist cancer cell migration along nerves but also support nerve growth towards pancreatic cancer cell colonies. Pancreatic stellate cells can also secrete hepatocyte growth factor (HGF) by activating the HGF/c-Met pathway.[299] Furthermore, CXCL12 secreted by CAFs can mediate NGF expression, enhance neurite outgrowth, and promote cancer cell migration and invasion through activation of the CXCL12/CXCR4 axis.[300]

The stressful environment of the tumor microenvironment influences its innervation. Cancer progression leads to the formation of a characteristic acidic, hyperglycemic, and hypoxic microenvironment around the tumor. Therapeutic agents may damage normal cells, causing cellular stress. These features collectively shape the stressful peritumoral environment, which also influences the process of tumor hijacking of nerves. The peritumoral acidic environment and acidosis facilitate the shift of cancer cells from glucose-based energy production (glycolysis) to more efficient energy generation via mitochondrial respiration.[301] Recent studies indicate that glycolysis is significantly upregulated in CAFs, creating a high-lactate tumor microenvironment that favors cancer progression. CAF-derived lactate is taken up by tumor cells, promoting histone H3K18 lactylation. Lactate-induced epigenetic modifications activate the transcription of nerve invasion-related genes (such as L1CAM and SLIT1), thereby driving PNI in pancreatic cancer.[238] Hyperglycemia promotes neural remodeling and induces perineural infiltration. In cancer patients, due to the "Warburg effect," direct destruction of pancreatic β-cells by cancer cells or the secretion of hyperglycemic hormones by cancer cells may lead to elevated blood glucose levels. In this process, hyperglycemia increases the secretion of NGF by pancreatic cancer cells, thereby enhancing axonogenesis and further promoting PNI through dependent demyelination and axon degeneration.[302] Additionally, hyperglycemia inhibits the migration of Schwann cells and promotes neural regeneration responses, ultimately reinforcing tumor innervation. In hypoxic environments, hypoxia-inducible factor-1α (HIF-1α) accumulates within cells. The HIF-1α complex binds to hypoxia response elements (HREs) of specific genes, directly activating EMT and upregulating the expression of TGF-β and its receptors, driving EMT through the SMAD signaling pathway. Furthermore, hypoxia induces the secretion of exosomes, which promote M2 macrophage polarization via let-7a miRNA, shaping the tumor microenvironment.

Surprisingly, the effects of treatment may also aid tumors in hijacking nerves. Treatment with the common chemotherapeutic agent 5-fluorouracil further exacerbates endoplasmic reticulum stress and the secretion of pro-brain-derived neurotrophic factor, ultimately promoting axonogenesis.[303,304] In fact, endoplasmic reticulum stress levels increase after chemotherapy and play a role in protecting cancer cells.

PRECLINICAL MODELS FOR STUDYING NEURON TUMOR INTERACTIONS

Neuron–tumor interaction is at the frontier of current oncology research, whose core lies in revealing the bidirectional regulatory mechanisms between the nervous system and tumor cells. Elucidating the neuron–tumor crosstalk, especially the complex mechanisms by which tumors actively hijack the nervous system, relies heavily on a series of continuously evolving preclinical models.[305]

Preclinical research models are mainly categorized into in vitro and in vivo systems. In vitro models include commercial tumor cell lines, patient-derived cell lines (PDC), and patient-derived organoids (PDO); commonly used in vivo models comprise cell line-derived xenografts (CDX), patient-derived xenografts (PDX), humanized immune-deficient mice (HIS mice), and genetically engineered mouse models (GEMMs), among others.[306]

Commercial tumor cell lines feature easy manipulation, low cost, and high stability, making them suitable for basic molecular mechanism studies and preliminary high-throughput drug screening. However, they exhibit low tumor fidelity and limited clinical relevance, and thus cannot serve alone as a reliable basis for pharmacodynamic evaluation.[306]

As a classic in vitro model, patient-derived cell lines (PDC) are frequently used for large-scale drug screening and signaling pathway research, yet they

fail to recapitulate the complex composition of the in vivo tumor microenvironment, posing significant limitations in immunotherapy-related studies. Furthermore, long-term in vitro passage tends to induce genetic drift, leading to deviations between cellular genotypes and primary tumors, further reducing their clinical translational value.[307,308]

Leveraging three-dimensional culture structures, patient-derived organoids can simulate tumor histomorphology and microenvironment to a certain extent, demonstrating high application value in personalized drug screening and precision medicine research.[309,310] Nevertheless, the PDO culture system is costly and cumbersome to operate, and still cannot fully replicate key microenvironmental components such as immune cell infiltration, vascular networks, and stromal interactions in vivo, rendering it unsuitable for high-throughput screening scenarios.[311]

Cell line-derived xenograft models are commonly employed for early in vivo efficacy evaluation, but the cell lines used have undergone long-term passage, resulting in genetic backgrounds and phenotypic characteristics that deviate significantly from primary tumors, lacking tumor heterogeneity and tissue complexity.[312,313] Meanwhile, constructed using immune-deficient mice, CDX models cannot reproduce tumor–immune crosstalk and are therefore inappropriate for assessing the efficacy of immunotherapeutic agents.[314,315]

Patient-derived xenograft models can well preserve the genetic heterogeneity and microenvironmental features of patient tumors, making them applicable for exploring personalized therapies and dissecting drug resistance mechanisms.[316,317] However, these models feature long construction cycles, high costs, and limited modeling success rates, rendering them unsuitable for high-throughput screening. They also rely on immune-deficient mouse hosts, failing to mimic anti-tumor immune responses and thus being inapplicable for immunotherapy evaluation.[318]

Humanized immune system mice have become an important tool for tumor immunotherapy research, especially immune checkpoint inhibitor studies, by reconstructing the human immune microenvironment.[319] However, issues such as incomplete immune reconstitution and interspecies immunophysiological differences may compromise the clinical translational efficacy of research findings.[320] Meanwhile, their high modeling and breeding costs and complex operations also limit their application in large-scale screening.

Genetically engineered mouse models can simulate the molecular processes of tumorigenesis and progression through precise gene editing, suitable for studying tumor pathogenesis and developing targeted drugs.[321] Nonetheless, these models require long construction cycles and high technical difficulty, and their clinical relevance remains to be improved due to

Table 2. Clinical trials of drugs targeting tumor-nerve interaction pathways.

No.	Therapeutic Category	Target/Drug	Indication	Trial Phase	Primary Endpoint	Trial number	Current Status
1	Dopamine Receptor Antagonist	ONC201 (DRD2/3 antagonist)	Glioblastoma (GBM) / H3 K27M-mutant glioma	Phase1/ 2	OS, DOR, ORR	NCT03295396 NCT03416530 NCT02525692 NCT05392374 NCT03134131 NCT05009992 NCT05580562 NCT03034200	Multiple studies (2022-2024) confirmed safety and preliminary efficacy as monotherapy and in combination. The first systemic therapy to receive FDA accelerated approval for the treatment of H3K27M-mutant diffuse midline glioma (DMG).
2	Dopamine Receptor Antagonist	ONC206 (DRD2/3 antagonist)	High-grade glioma	Phase 1	DLT MTD	NCT04541082 PNOC 023	Currently being explored in a broader range of CNS tumors and peripheral solid tumors (e.g., ovarian cancer, endometrial cancer, TNBC)
3	β-Adrenergic Receptor Blocker	Propranolol	Melanoma, breast cancer, colon cancer	Phase 1/2/3	ORR	NCT03384836 NCT03919461 NCT01504126 NCT01308944 NCT00888797 NCT00502684 NCT01847001 NCT03838029 NCT04848519 ChiCTR2500108957 ACTRN12615000895500	Multiple trials ongoing Multiple studies showed enhanced immunotherapeutic efficacy when combined with PD-1 inhibitors
4	β-Adrenergic Receptor Blocker	Atenolol	Multiple tumor types	Retrospectiv e Study	Mortality rate	-	Evidence primarily derives from retrospective studies, small prospective trials, and preclinical research; large-scale Phase III confirmatory clinical trials are still lacking.
5	Muscarinic Receptor Agonist	Bethanechol	PDAC	Phase 0	Impact on tumor activity	NCT03572283	As a direct antitumor agent, it has only shown immunomicroenvironment-modulating potential in a Phase 0 pancreatic cancer study
6	ADAM10/17 Inhibitor	INCB7839	Triple-negative breast cancer (TNBC) DLBCL Pediatric high-grade glioma	Phase 1/2	ORR PFS MTD safety and antitumor activity	NCT00864175 NCT01254136 NCT02141451 NCT04295759 NCT00820560	The agent was evaluated across multiple Phase I/II clinical trials for efficacy and safety in HER2-positive breast cancer, diffuse large B-cell lymphoma (DLBCL), and pediatric high-grade glioma, among other indications. However, its global development has been discontinued due to safety concerns, notably thrombotic risk

Table 2. *(Continued)*

No.	Therapeutic Category	Target/Drug	Indication	Trial Phase	Primary Endpoint	Trial number	Current Status
7	NGF Inhibitor	Tanezumab	Bone metastasis pain	Phase 3	Pain score improvement	NCT02609828	Phase 3 randomized double-blind placebo-controlled trial demonstrated significant pain relief; safety concerns regarding rapidly progressive osteoarthritis (RPOA) limit clinical application
8	TRK Inhibitor	Larotrectinib (LOXO-101)	TRK fusion-positive solid tumors	Phase 1/2	ORR DOR	NCT02122913 NCT02637687 NCT02576431	FDA-approved (2018) Updated data demonstrated long-term efficacy and durable responses
9	TRK Inhibitor	Entrectinib (RXDX-101)	NTRK/ROS1/ALK fusion-positive tumors	Phase 1/2/3	ORR, CNS activity	NCT02097810 NCT02568267 NCT02650401 NCT05770544 NCT04551495 CTR20201930（China）	FDA-approved (2019)1) NTRK fusion-positive solid tumors in adults and children (≥12 years); 2) ROS1-positive NSCLC in adult patients Updated data demonstrated robust CNS penetration and intracranial efficacy
10	TRK Inhibitor	Selitrectinib (LOXO-195)	NTRK-acquired resistance tumors	Phase 1/2	ORR, safety	NCT03215511 NCT04275960 NCT03206931	Significant efficacy in patients resistant to first-generation TRK inhibitors Selitrectinib has officially entered the China Phase 1 clinical stage
11	TRK Inhibitor	Repotrectinib (TPX-0005)	NTRK fusion-positive and ROS1+ NSCLC	Phase 1/2	ORR DOR PFS	NCT03093116	FDA Accelerated Approval granted November 2023 (ROS1+ NSCLC)
12	Vagus Nerve Stimulation (VNS)	VNS device	Head and neck tumors	Phase 2/3	Cancer pain, quality of life Post-radiotherapy fatigue	NCT05543239 NCT06817161 ChiCTR2300072800 NCT04563013	No high-quality clinical evidence currently confirms that VNS can directly inhibit tumor growth; its primary value lies in supportive care
13	NK1 Receptor Antagonist	Aprepitant	TNBC	Retrospective Study	DFS OS	-	First large real-world dataset to suggest that aprepitant may improve survival outcomes in early-stage breast cancer patients (particularly refractory subtypes), providing a basis for subsequent prospective clinical trials
14	AMPA Receptor Antagonist	Perampanel	Recurrent/Progressive Glioblastoma	Phase 2	Efficacy	PerSurge (NOA-30）	PerSurge (NOA-30) is the world's first clinical trial targeting neuron-glioma synapses; no results published as of 2026
15	Inhibition of Gap Junction-Mediated Intercellular Communication and Disruption of Tumor Microtube (TM) Network	Meclofenamic acid	Patients with recurrent MGMT-methylated glioblastoma	Phase 1/2	Safety efficacy	EudraCT2021-000708-39	World's first clinical trial targeting the GBM tumor microtube (TM) network; evaluates whether meclofenamic acid, as the first clinically feasible drug targeting the TM network, can improve outcomes in refractory recurrent GBM.
16	Combination Therapy	Two-, Three-, or Four-Drug Regimens (TMZ + Memantine + Mefloquine + Metformin)	Adults with newly diagnosed glioblastoma who have completed chemoradiotherapy	Phase 1/2	OS, PFS Safety	NCT01430351	Terminated results not yet published

OS: Overall Survival; DOR: Duration of Response; ORR: Objective Response Rate; PFS: Progression-Free Survival; DLT – Dose-Limiting Toxicity; MTD: Maximum Tolerated Dose.

biological differences between humans and mice. In addition, systemic gene knockout or mutation often causes phenotypic alterations in multiple organs, making it more challenging to study tumor mechanisms in specific tissues.[322,323]

Research on neuron–tumor crosstalk mechanisms and subsequent clinical translation necessitates the combination of different models to overcome the limitations of single models. The combined application of multiple models facilitates research on the mechanisms of "cancer neuroscience" and provides more reliable evidence for clinical translation.

THERAPEUTIC PROSPECTS

We have summarized drugs targeting tumor-nerve interaction pathways that have entered the clinical trial stage, and provide perspectives on future challenges and directions in clinical translation. (Table 2)

CONCLUSION

In summary, this comprehensive review elucidates the complex interplay between the nervous system and tumor biology, encompassing the roles of both the CNS and the PNS in cancer progression.[88] The findings emphasize

the multifaceted roles of neuro-immune interactions in cancer progression and treatment resistance, highlighting the significance of neural regulation in shaping the tumor microenvironment and immune response, as well as the potential of targeting neuro-immune signaling pathways for therapeutic intervention.[104,261] Notably, tumors are not only regulated by the nervous system but can also actively reshape and hijack the structure and function of the nervous system, forming a positive feedback loop that promotes their own growth and immune evasion.[7] Despite these groundbreaking advances in the field of nerve-tumor-immune interactions, numerous issues and challenges remain: First, the mechanisms of neural regulation exhibit substantial heterogeneity across different tumor types, stages, and microenvironmental contexts, and the roles of certain pathways (e.g., the parasympathetic nervous system) remain controversial. Second, the current body of research evidence is largely derived from preclinical studies relying on animal models, which differ from the true pathophysiological landscape of human nerve-tumor-immune interactions, resulting in limited clinical translation efficiency. Third, neural interventions lack sufficient targeting specificity, which may disrupt normal neural functions and carry a high risk of adverse effects. Fourth, the interplay between treatment-induced nerve injury and tumor progression remains poorly understood, impacting long-term survival and quality of life in patients.

In the future, further systematic dissection of the regulatory heterogeneity of the central and peripheral nervous systems across different tumor types and disease stages is warranted. By leveraging viral neural tracing,[324,325] optogenetics, chemogenetics, and electrophysiological techniques, the specific neural circuits driving tumor progression should be clearly defined, with the interference from normal physiological functions effectively excluded. Combined with spatial multi-omics, in vivo two-photon imaging, and other cutting-edge technologies, in-depth investigations should be conducted to elucidate the spatiotemporal distribution and dynamic interplay of nerves, tumor cells, and immune cells within the TME. Meanwhile, epigenetics, metabolic reprogramming, and mitochondrial crosstalk should be integrated to dissect the roles of tumor-derived exosomes and neurotransmitter metabolism in neural remodeling, thereby unraveling the molecular programs through which tumors hijack the nervous system.[326] These programs encompass key biological processes, including axonogenesis, neoneurogenesis, the reprogramming of sensory nerves toward an adrenergic phenotype, mitochondrial transfer, and metabolic hijacking. Additionally, the bridging roles of Schwann cells, enteric glial cells, and cancer-associated fibroblasts in the nerve–tumor–immune axis need to be clarified, which will provide a solid theoretical foundation for the development of strategies to block perineural invasion and reverse immunosuppression. At the clinical translation level, efforts should be expedited to establish models based on induced pluripotent stem cell (iPSC)-derived organoids, humanized nerve–tumor–immune models, and humanized immune system mice, so as to enhance the translational efficiency from basic research to clinical practice. Non-invasive biomarkers integrating neuroimaging, liquid biopsy, and spatial multi-omics should be developed to dynamically evaluate the degree of tumor innervation, immune status, and therapeutic response. Moreover, combination strategies involving neural-targeted agents (e.g., receptor antagonists, protease inhibitors, β-blockers) with immune checkpoint inhibitors, chemotherapy, and radiotherapy should be systematically investigated, and dosing regimens should be optimized to overcome therapeutic resistance. Furthermore, tumor microenvironment-responsive delivery systems and locally precise neuromodulation technologies should be developed to block pro-tumorigenic neural signals while maximizing the preservation of normal neural physiological functions and minimizing treatment-related neurotoxicity. In addition, multidisciplinary integration of neuroscience, oncology, immunology, and biomedical engineering is essential to ultimately achieve precision anti-tumor therapy targeting the nerve–tumor–immune interactive network. This approach is expected to break through the bottlenecks of conventional anti-tumor treatments and provide a novel pathway for improving the prognosis and quality of life of patients with malignant tumors.

The insights provided here pave the way for integrating the mechanisms and therapeutic strategies of the tripartite interaction between the tumor microenvironment, nervous system, and immune system, offering new hope for improving outcomes in patients with various malignancies.

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AUTHOR CONTRIBUTIONS

AN.S, ZY.Z and ST.Z wrote the manuscript together. JB.H and GH.W designed the plans for research studies. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.