Chinese Medical Journal®

Neurobiology of cancer: Unraveling the roles of the nervous system in tumor initiation, progression, and therapeutic

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Abstract

Accumulating evidence highlights a complex interplay between the nervous system and cancer; the nervous system has a significant influence on tumor progression. This review explores the burgeoning field of neuro-oncology, focusing on the nervous system's role in tumor initiation, growth, invasion, metastasis, and treatment response. In most cases, the nervous system interacts with the tumor microenvironment (TME) through its extensive and highly intricate network at both the local and systemic levels, thereby promoting malignant behaviors such as tumor growth, invasion, and metastasis. Conversely, in certain tumor types, neural–tumor interactions may suppress tumor progression. This bidirectional regulatory phenomenon highlights the complex and diverse role of the nervous system in tumor development. Within the TME, the nervous system influences tumor progression through multiple mechanisms, including synaptic connections, paracrine signaling, and immune regulation. Studies show that in brain tumors, neurons and glial cells can promote tumor growth and treatment resistance through neurotransmitter release, synaptic signaling, and inflammatory modulation, whereas in peripheral tumors, autonomic and sensory nerve activity also regulates tumor progression. Understanding these interactions enhances our comprehension of tumor biology and enables the development of innovative therapeutic strategies targeting neuro–cancer interfaces. This interdisciplinary approach, integrating neuroscience, immunology, and oncology, provides insights into cancer–nervous system dynamics, and holds promising potential to advance the development of effective anticancer therapies.

Keywords: Cancer neuroscience; Neuro-oncology; Tumor microenvironment; Cancer treatment; Neuro–immune interaction; Tumor innervation

Introduction

Cancer neuroscience is an emerging interdisciplinary field that studies the bidirectional interactions between cancer and the nervous system. It seeks to understand how neural components regulate tumor biological processes and how tumors in turn affect neural structure and function.[1,2] Several studies and reviews have confirmed the critical role of the nervous system in regulating tumor progression, with particular emphasis on the neuro–immune–tumor axis and the emerging concept of neural-targeted cancer therapy, both of which have become major research frontiers in recent years.[2–4] The extensive and highly integrated neural network spans the entire body, including the tumor microenvironment (TME), and influences multiple stages of tumor progression.[1] Against this backdrop, the present review systematically summarizes the regulatory mechanisms through which the nervous system modulates the progression of diverse cancer types, provides an in-depth analysis of the bidirectional interactions between neural and tumor cells, and highlights current strategies targeting neural regulation. By integrating shared principles across different tumor types, this work aims to offer a more comprehensive perspective for advancing the field of cancer neuroscience and provide conceptual guidance for the paradigm shift in oncology—from traditional "local cytotoxicity" toward a "systemic regulatory therapy" framework.

The nervous system's influence on cancer manifests through direct interactions between neurons, neuroglia, and cancer cells within the brain TME, and indirect mechanisms such as paracrine signaling, neuro–cancer synaptic connections, and modulation of immune cell function.[4] These intricate interactions shape the inflammatory milieu within tumors—promoting growth and metastasis—and affect treatment response.[5] Conversely, cancer can impact the nervous system by tumor invasion

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000004144

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Chinese Medical Journal 2026;XX(XX)
Received: 24-12-2025; **Online:** 16-06-2026 **Edited by:** Ting Gao

and remodeling of neural structures, while cancer therapy can cause direct or indirect damage.[6]

In recent years, advances in cancer neuroscience have brought new hope for treating refractory malignant tumors, while also deepening our understanding of how the nervous system regulates normal organ function and immune responses.[6,7] However, current research in this field remains markedly limited: most studies focus on specific cancer types, lacking systematic comparisons of neural regulatory mechanisms across different tumors, which hinders the identification and integration of common pathways. Moreover, although preclinical studies have uncovered various neural-related targets, their translation to clinical applications faces multiple challenges. Issues such as drug specificity, delivery systems, therapeutic windows, and the inherent complexity of the nervous system continue to impede progress.

Therefore, advancing this field requires interdisciplinary collaboration among neuroscience, developmental biology, immunology, and tumor biology. By systematically elucidating the complex interactions between the nervous system and cancer, it may be possible to develop broader-spectrum and more feasible neural-targeted therapeutic strategies, paving the way for new directions in clinical intervention.

Impact of the Central Nervous System (CNS) in Intracranial Tumors

The CNS primarily comprises neurons and neuroglia. Beyond their fundamental roles in neural function, neurons engage in intricate interactions with tumor cells, influencing tumor initiation, progression, and response to therapy. These interactions predominantly promote tumor initiation and progression [Supplementary Figure 1, http://links.lww.com/CM9/C916].

The CNS can influence the progression of primary intracranial tumors and their response to therapy. For instance, in optic gliomas, visual nerves facilitate tumorigenesis by modulating neuroligin 3 (NLGN3) shedding triggered by neurofibromatosis type 1 (NF1) mutations.[8] In a mouse model of optic pathway glioma (OPG), visual nerve activity was found to stimulate tumor growth.[9] Similarly, in a low-grade glioma (LGG) mouse model based on the replication-competent avian sarcoma-leukosis virus (RCAS)/Ntva system, the regulatory factor semaphorin-4F (SEMA4F) promoted the spread of cancer cells along neural pathways by influencing projection neurons in the corpus callosum of primary glioblastoma (GBM).[10] In high-grade gliomas of the olfactory bulb, olfactory-stimulated neuronal activity drives tumorigenesis through insulin-like growth factor 1 (IGF1), mediating an olfaction-dependent mechanism.[11]

The nervous system also plays a role in regulating tumor resistance to therapy. Astrocytes enhance GBM resistance to radiotherapy or chemotherapy by interacting with tumor cells through gap junctions, which increase intracellular calcium levels.[12] Similarly, neurons promote therapeutic resistance by inducing a neuro-mesenchymal transition in GBM stem cells through exosomes, thereby augmenting cancer cell tolerance to radiotherapy.[13]

Furthermore, neural innervation can also regulate brain tumor metastasis. Astrocytes, the predominant neuroglial cells in the CNS, release various growth factors (such as fibroblast growth factor [FGF], hepatocyte growth factor [HGF], and transforming growth factor beta [TGF-β]), promoting glioma proliferation and invasion.[14] In hypoxic TME models, astrocytes enhance glioma invasion by increasing C-C motif chemokine ligand 20 (CCL20) release, which induces hypoxia-inducible factor (HIF-1α) expression in tumor cells.[15] However, astrocyte-derived exosomes also exhibit antitumor potential by suppressing the proliferation, migration, and invasion of GBM cells.[16] Microglia, another key component of neuroglia, are involved in neural regulation and synaptic plasticity and in various cognitive functions such as learning and memory.[17] However, activated microglia may exhibit immunosuppressive properties, creating a microenvironment conducive to tumor growth.[18] Concurrently, some studies have found that microglia may also exert antitumor effects—for instance, by activating natural killer (NK) cells and T cells, thereby effectively suppressing brain metastases of breast cancer.[19] A previous study showed that neurons, in conjunction with astrocytes, can inhibit brain metastasis; plasminogen activators produced by astrocytes convert neuron-derived plasminogen into plasmin. On the one hand, it promotes Fas ligand (FasL) release from astrocytes to induce apoptosis in cancer cells, and on the other hand, cleaves and inactivates L1 cell adhesion molecule (L1CAM) on the surface of cancer cells, thereby disrupting their attachment to brain vasculature.[20] Dopaminergic neurons produce dopamine, a neurotransmitter that influences neural functions such as emotion and reward. Although numerous studies have shown that dopamine signaling pathways can promote cancer, a few studies have reported that dopamine exerts anti-tumor effects in the brain.[21,22] In malignant gliomas, dopamine exerts antitumor effects and inhibits invasion and metastasis by regulating angiogenesis, inducing autophagy and apoptosis, and promoting the polarization of macrophages toward the M1 phenotype.[22,23]

In summary, the CNS directly and indirectly influences tumorigenesis and progression. Targeting CNS components may represent a viable strategy for treating intracranial tumors.

Regulatory Role of the Nervous System in the Progression of Peripheral Tumors

The nervous system plays a pivotal role in the progression of extracranial tumors [Figure 1]. Notably, the CNS primarily influences tumors through "systemic/indirect" mechanisms. For example, activation of the hypothalamic–pituitary–adrenal (HPA) axis and autonomic pathways elevates glucocorticoids and catecholamines, which in turn alter systemic immunity, inflammation, and metabolism to influence tumor growth and metastasis. The CNS may also modulate tumor progression indirectly by altering the homeostasis and metabolic activity of the gut microbiota.[24,25] In contrast, the peripheral nervous system (PNS) exerts its effects more directly through

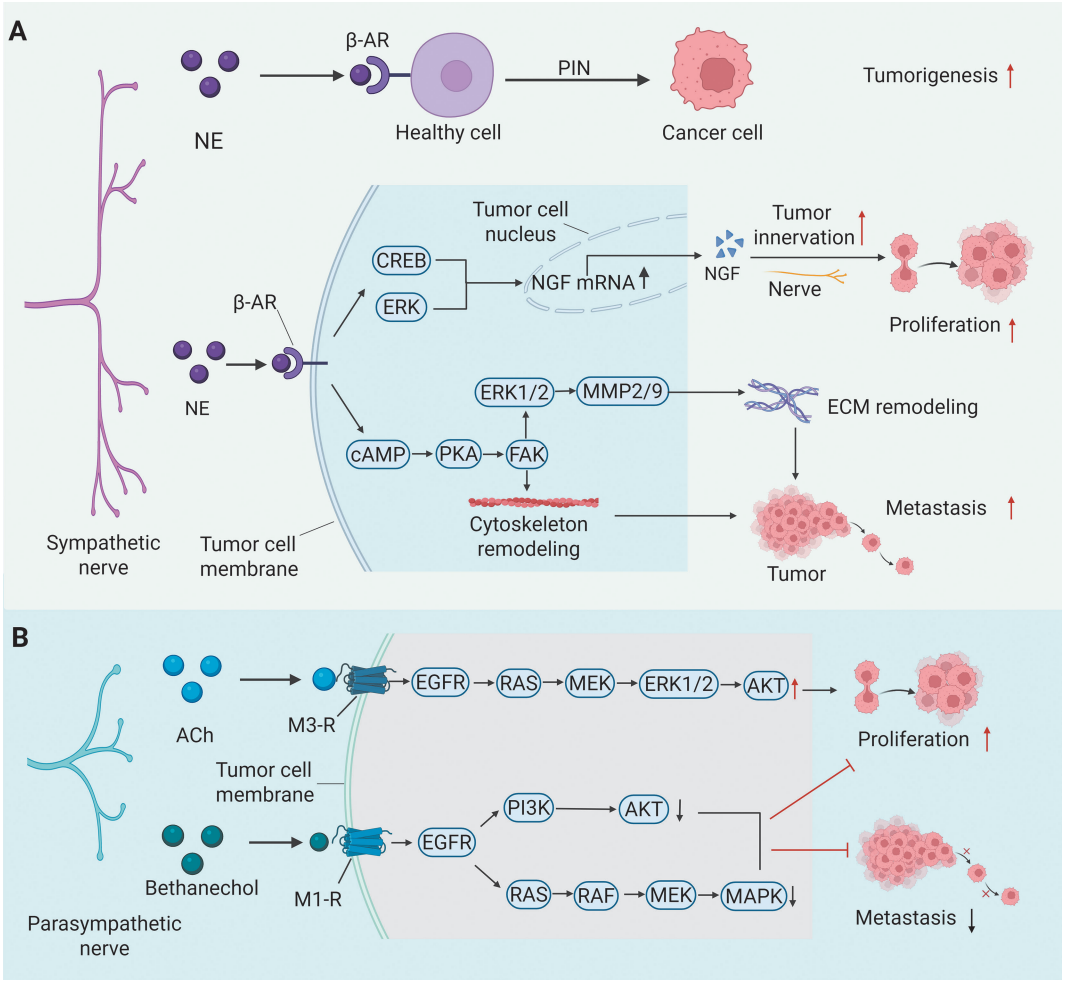

Figure 1: Impact of the sympathetic and parasympathetic nervous systems on cancer initiation and progression. (A) Impact of the SNS on tumor initiation and progression. The SNS may promote tumor initiation by releasing NE, which induces PIN. Additionally, NE can bind to β2/3-ARs on cancer cells, enhancing the secretion of NGF, thereby increasing tumor innervation and promoting tumor growth. Moreover, NE binding to β2-AR on cancer cells activates the cAMP-PKA signaling pathway, leading to cytoskeletal and ECM remodeling, which facilitates tumor invasion and metastasis. (B) Impact of the parasympathetic nervous system on tumor progression. The parasympathetic nervous system may contribute to tumor progression by releasing ACh, which binds to M3 muscarinic receptors on tumor cells, activating the EGFR signaling pathway and promoting cancer cell proliferation. Meanwhile, bethanechol, a muscarinic receptor agonist, can inhibit tumor growth and invasion by suppressing the MAPK and PI3K/AKT signaling pathways. ACh: Acetylcholine; AKT: Protein kinase B; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; β2/3-AR: β2/3 adrenergic receptor; cAMP: Cyclic adenosine monophosphate; CREB: cAMP response element-binding protein; ECM: Extracellular matrix; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinase; FAK: Focal adhesion kinase; MAPK: Mitogen-activated protein kinase; MEK: Mitogen-activated protein kinase kinase; MMP: Matrix metalloproteinase; MR: Muscarinic receptor; NE: Norepinephrine; NGF: Nerve growth factor; NMDAR: N-methyl-D-aspartate receptor; PI3K: Phosphoinositide 3-kinase; PIN: Prostatic intraepithelial neoplasia; PKA: Protein kinase A; RAF: Rapidly accelerated fibrosarcoma kinase; RAS: Rat sarcoma; SNS: Sympathetic nervous system.

local tumor innervation, acting on tumor cells and the TME—including vasculature, immune infiltrates, and stromal components—to regulate proliferation, invasion, and immune evasion.[26] The effect of the sympathetic nervous system (SNS) is highly context-dependent across different tumor types: while it primarily promotes tumor progression in breast and prostate cancer, under specific conditions—such as activation of the brain's reward system—it can exert antitumor effects by modulating the immune microenvironment in models of pancreatic cancer, melanoma, and lung cancer.[27] Similarly, the parasympathetic nervous system has a tumor-type-specific regulatory role: it promotes the growth of gastrointestinal tumors while inhibiting the proliferation and metastasis of pancreatic cancer.[28] Notably, the sensory nervous system and its secreted neurotrophic factors play a non-negligible role in shaping the peripheral TME through distinct neuro-tumor crosstalk mechanisms.

Here, we discuss the influence of the nervous system on peripheral tumors using breast, prostate, pancreatic, gastrointestinal cancers, oral cancer, melanoma, and lung cancer as representative examples.

Breast cancer

Studies show that the sympathetic and sensory nervous systems promote breast cancer progression by stimulating cancer cell growth and modulating the tumor immune response. Conversely, the parasympathetic nervous system may inhibit breast cancer progression by regulating the immune response.

A negative correlation between sympathetic nerve density and patient prognosis has been observed in breast cancer, suggesting the involvement of SNS in promoting tumor progression[29] via norepinephrine (NE) and epinephrine

(E). E promotes breast cancer cell proliferation via α2-adrenergic receptors (α2-ARs),[30] and interacts with β2-ARs to phosphorylate the pro-apoptotic protein B-cell lymphoma 2 (BCL2)-associated agonist of cell death (BAD), thereby reducing cancer cell sensitivity to apoptosis.[31] Moreover, β-adrenergic signaling induces cytoskeletal rearrangements and matrix metalloproteinase (MMP) production, enhancing tumor invasion.[32] High levels of β2-AR are associated with lymph node metastasis and poor prognosis in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer.[33] The SNS also modulates cytokine release within the TME, influencing the number and function of infiltrating immune cells and promoting the expression of metastasis-associated genes.[34,35]

Neural signaling may also facilitate breast cancer metastasis. A previous study showed that 4T1 breast cancer cells significantly increased neuronal mitochondrial mass and facilitated the transfer of mitochondria from neurons to cancer cells in a nerve–cancer co-culture model, thereby supporting cancer cell survival and colonization during metastasis.[36] Co-culturing triple-negative breast cancer (TNBC) cells with dorsal root ganglia sensory neurons significantly increased their metastasis to lungs.[37] This effect is partly mediated by increased neuropeptide Substance P (SP) release via calcium signaling in sensory neurons, promoting tumor growth, invasion, and metastasis through tachykinin receptor 1 activation.[38] Additionally, astrocytes produce transforming growth factor-β2 (TGF-β2), which promotes brain metastasis of TNBC cells via the TGF-β2/angiopoietin-like 4 axis.[39] Cancer cells also form pseudo-tripartite synapses with N-methyl-d-aspartate receptors and glutamatergic neurons, facilitating the colonization of breast cancer cells in the brain.[40]

However, the role of neural innervation in breast cancer is multifaceted. Although the parasympathetic nervous system does not directly innervate the mammary gland, it may inhibit tumor progression by regulating immune responses.[41] Evidence suggests that the density and activation of the parasympathetic nervous system can inhibit breast cancer progression.[42,43] Parasympathetic stimulation can suppress PD-1 expression but increase interferon-γ (IFN-γ) on tumor-infiltrating lymphocytes, thereby enhancing antitumor immunity.[44] Zhang *et al*[45] observed that vagus nerve stimulation promotes antitumor immunity by enhancing the accumulation and activity of $CD8^+$ T cells and NK cells, while inhibiting myeloid-derived suppressor cells (MDSCs). Additionally, vagus nerve activity lowered proinflammatory cytokines (such as interleukin-1 beta [IL-1β] and tumor necrosis factor-alpha [TNF-α]) in serum and alleviated tumor and local inflammatory infiltration.[45]

Chronic stress-induced neuroendocrine alterations and disruptions in gut microbiota homeostasis also influence breast cancer progression. For instance, chronic stress-mediated glucocorticoid release enhances the formation of neutrophil extracellular traps in the lung, creating a pro-metastatic microenvironment that facilitates breast cancer lung metastasis.[46] Psychological stress markedly reduces the abundance of gut bacteria, such as *Akkermansia muciniphila*, resulting in decreased levels of the short-chain fatty acid (SCFA) butyrate, ultimately driving breast cancer cells toward a cancer stem-like state associated with tumor initiation, metastasis, therapy resistance, and recurrence.[47] In female patients with breast cancer with depression, reduced acetate abundance is a key factor linked to diminished tumor-infiltrating $CD8^+$ T cells and increased risk of metastasis.[48]

Prostate cancer

In prostate tumors and their surrounding normal tissues, the density of sympathetic and parasympathetic nerve fibers is closely associated with poor clinical outcomes.[2,49] Sympathetic and parasympathetic nerves have differing effects on prostate tumor progression as they affect different stages and processes. Sympathetic nerves play a promotive role in the early stages of prostate tumor development. In rats, α-adrenergic agonists can induce both atypical prostatic hyperplasia and tumor formation.[50] Sympathetic nerves promote prostatic intraepithelial neoplasia (PIN) and tumor angiogenesis through β-ARs.[2,51] Depression may activate the SNS-mediated cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA)-focal adhesion kinase (FAK) pathway, thereby exacerbating the invasiveness of prostate cancer.[52] Sympathetic nerve ablation inhibits tumor progression by inducing apoptosis in the PIN region and reducing tumor growth induced by NE.[53] However, progenitor cells originating from the CNS can induce new adrenergic innervation within prostate tumors, further facilitating metastatic dissemination.[54]

In contrast, parasympathetic nerves may facilitate tumor invasion and metastasis in the later stages of prostate cancer.[55] Blocking parasympathetic innervation effectively suppressed tumor growth and metastasis in mouse models.[2] Oliveira-Barros *et al*[56] hypothesized that prostate cancer cells acquire more aggressive and invasive phenotypes after interacting with astrocytes, which may represent a key mechanism underlying brain metastasis.

Pancreatic cancer

The pancreas is extensively innervated by sympathetic nerve fibers, and pancreatic cancer cells express receptors for sympathetic neurotransmitters, suggesting that pancreatic cancer may be sensitive to sympathetic signaling. Indeed, the SNS exhibits dual roles in regulating pancreatic cancer progression. Chronic stress accelerates cancer progression through nerve growth factor (NGF)-brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase (Trk) signaling, increasing sympathetic innervation and NE accumulation.[57] Perineural invasion (PNI), the phenomenon of cancer cell invasion along nerves, is associated with poor prognosis in pancreatic cancer.[58–60] Although SNS promotes PNI via the NE-β-AR/PKA/signal transducer and activator of transcription 3 (STAT3) pathway,[61] it can also enhance immune function, thereby suppressing tumor progression. Ablation of sympathetic innervation increases $CD163^+$ macrophage infiltration, promoting tumor growth and metastasis.[62] Moderate stress-induced

SNS activation boosts the antitumor activity of NK cells, enhancing their tumor infiltration.[63]

The parasympathetic nervous system inhibits pancreatic cancer progression. Subdiaphragmatic vagotomy accelerates pancreatic cancer growth and reduces patient survival.[64,65] High expression of the parasympathetic neurotransmitter receptor muscarinic acetylcholine receptor (M3R) correlates with poor prognosis in pancreatic cancer patients.[66,67]

Neurotrophic factors and sensory nerves also contribute to pancreatic cancer progression. Artemin promotes cancer cell invasion along pancreatic nerves.[68] Nociceptive sensory neurons interact with cancer-associated fibroblasts through calcitonin gene-related peptide (CGRP) and NGF, which suppress the infiltration and cytotoxic function of NK cells, thereby promoting the progression of pancreatic ductal adenocarcinoma (PDAC) and cancer-related pain.[69] Ablation of sensory neurons slows PDAC growth.[70]

Gastrointestinal tract cancers

The gastrointestinal tract is richly innervated, and autonomic signaling plays a critical role in its function. Neural innervation can influence the progression and prognosis of gastrointestinal cancers.

In colorectal cancer (CRC), the degree of PNI positively correlates with patient survival.[71] Parasympathetic innervation may promote gastrointestinal cancer progression. For instance, acetylcholine (ACh) activates the M3R receptor to stimulate the epidermal growth factor receptor (EGFR) pathway, inducing extracellular signal-regulated kinase 1/2 (ERK1/2) and protein kinase B (AKT, also known as PKB) phosphorylation, which drives gastric cancer cell proliferation.[72] Vagotomy suppresses tumor formation, enhances apoptosis, and improves the efficacy of 5-fluorouracil (5-FU) in gastric cancer xenograft models.[73,74] In CRC, overexpression of the *M3R* gene enhances cancer cell proliferation, migration, and invasion.[75] Schwann cells are enriched in CRC tissues and are associated with tumor metastasis and poor prognosis, a process potentially mediated by Schwann cell-derived NGF.[76] A review by Xu *et al*[77] mentioned that the SNS promotes tumor proliferation and metastasis via inducing NE and E secretion. Specifically, NE activates the β-catenin signaling pathway, thereby enhancing the growth of CRC cells. Ach signaling plays a dual role by interacting with both tumor cells and immune cells.

Chronic stress can also regulate tumor progression by altering autonomic neural activity or disrupting gut microbial homeostasis. For example, chronic stress impairs intestinal stem cell stemness by activating the cholinergic enteric neural pathway, suggesting potential therapeutic targets for stress-related intestinal disorders.[78] Stress-induced elevation of adrenal hormones promotes CRC progression through the β2-AR/cAMP responsive element binding protein 1 (CREB1) signaling pathway.[79] Stress also activates the lateral septum—a key subcortical hub for emotional regulation—which remodels the activity of cholinergic enteric neurons and shifts gamma-aminobutyric acid (GABA) to the dominant neurotransmitter, thereby accelerating cancer progression.[80] Furthermore, chronic stress activates β-catenin signaling and reduces gut microbiota diversity, markedly increasing tumor burden, shortening colon length, and decreasing survival in CRC mouse models.[81]

Oral cancer

Most nerves in oral cancer are either sensory or a combination of sensory and other nerve types.[82] In mouse models of oral cancer, adrenergic nerve fibers have been shown to promote tumor growth, and increased nerve fiber density is significantly associated with poor clinical outcomes.[83] Schwann cells, a type of peripheral glial cell, facilitate cancer cell proliferation, migration, dissemination, and PNI in various cancers. In oral cancer, the presence of Schwann cells enhances tumor aggressiveness by promoting cancer cell proliferation, facilitating extracellular matrix (ECM) degradation, and modulating cellular metabolism.[84] Moreover, dietary intake of palmitic acid induces tumor-associated Schwann cells to secrete a specialized proregenerative ECM, thereby promoting oral cancer metastasis in mice.[85] Additionally, interactions between oral squamous cell carcinoma and Schwann cells may accelerate tumor progression and exacerbate cancer-related pain by enhancing the secretion of interleukin-6 and macrophage colony-stimulating factor, as well as by activating oxidative stress pathways.[86,87]

Melanoma

Melanoma-activated Schwann cells can remodel the TME by modulating the immune system and reorganizing the ECM, thereby promoting melanoma progression.[88] Interactions between nociceptive sensory neurons and melanoma cells lead to the release of CGRP, which induces functional exhaustion of cytotoxic $CD8^+$ T cells and impairs their tumor-eliminating capacity.[89] Moreover, NGF binds to the tropomyosin receptor kinase A (TrkA) expressed on melanoma cells, resulting in desensitization to IFN-γ signaling and subsequent dysfunction of both T cells and NK cells, thus enhancing the immunosuppressive milieu.[90]

Neural signaling is also closely associated with metastasis. Melanoma cells release extracellular vesicles enriched with NGF receptors, which disseminate through the lymphatic system and are taken up by lymphatic endothelial cells, thereby facilitating lymph node metastasis.[91] Granulocyte-derived lipocalin-2 induces inflammatory activation of astrocytes, leading to the recruitment of myeloid cells to the brain and promoting brain metastasis of melanoma.[92] Biermann *et al*[93] reported that cancer cells from melanoma brain metastases exhibit greater chromosomal instability and adopt a neuronal-like cell state to evade immune surveillance.

Lung cancer

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine subtype with a poor clinical prognosis.[94]

Numerous studies have demonstrated that cholinergic signaling significantly promotes the growth of SCLC.[95,96] Sympathetic neural signals enhance cancer cell proliferation by activating the PKA signaling pathway.[97] SCLC cells with neuroendocrine features can synthesize and secrete ACh, which facilitates the propagation of electrical activity between tumor cells, conferring sustained tumorigenic potential and enhanced metastatic capacity.[98] In non-small cell lung cancer (NSCLC), NGF induces neural infiltration, while neuron-derived serotonin (5-hydroxytryptamine, 5-HT) promotes glycolytic activity in NSCLC cells, thereby driving tumor metabolic reprogramming and exacerbating immunosuppression within the TME.[99] In addition, Schwann cells can promote epithelial–mesenchymal transition (EMT), invasiveness, and metastasis of lung cancer cells by activating the C-X-C motif chemokine 5 (CXCL5)/C-X-C motif chemokine receptor 2 (CXCR2)/phosphoinositide 3-kinase (PI3K)/AKT/glycogen synthase kinase-3 (GSK-3)β/Snail-Twist signaling pathway.[100]

Astrocyte-induced expression of metabotropic glutamate receptor 1 (mGluR1) in lung cancer cells leads to significant mGluR1-dependent signaling within the brain microenvironment, thereby promoting brain metastatic growth of lung cancer cells.[101] When co-cultured with neurons, lung cancer cells exhibit enhanced responsiveness to neurotransmitters such as GABA and dopamine. Both *in vitro* and *in vivo* experiments have confirmed that tumor cells can rely on neuron-secreted GABA to facilitate brain metastasis colonization.[102]

Psychological stress can also regulate tumor progression by reshaping the immune microenvironment. Stress upregulates HIF1A-AS3, which drives M2 macrophage polarization within tumor tissues and promotes lung cancer progression.[103] In a prospective cohort study of patients with lung cancer receiving immune checkpoint inhibitors, higher levels of emotional stress were associated with poorer clinical outcomes, suggesting that stress may impair the efficacy of immunotherapy.[104]

Other cancers

Beyond breast, prostate, pancreatic, gastrointestinal, oral, lung cancers, and melanoma, the nervous system broadly participates in the regulation of tumor initiation, invasion, metabolic reprogramming, and therapeutic response across many solid tumors. In cancers such as renal cell carcinoma (RCC), cervical cancer, and ovarian cancer, both autonomic and sensory neural signals modulate tumor cell behavior, shape the immune microenvironment, and influence treatment sensitivity, suggesting that neural regulation may represent a shared pathogenic network across diverse malignancies.

The kidneys receive dual innervation from the sympathetic and parasympathetic nervous systems. The renal autonomic nervous system plays a critical role in regulating immune responses and inflammation, processes that may indirectly influence the TME and progression of renal cancers.[105] Cutcliffe *et al*[106] reported that RCC tissues express multiple neuronal markers that may promote tumor progression by activating the PI3K/AKT signaling pathway. Sympathetic nerve density is increased in RCC compared with the normal kidney, accompanied by markedly elevated intratumoral NE.[107] Treatment of patient-derived tumor xenografts with propranolol reduces tumor growth and pulmonary metastasis.[108] α1-AR is overexpressed in RCC cells and promotes proliferation via the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) pathway.[109] β2-AR activation enhances tumor progression by inducing vascular endothelial growth factor (VEGF) secretion and suppressing $CD8^+$ T cell cytotoxicity.[110]

In cervical cancer, the neuropeptide neuromedin B (NMB) produced by tumor cells activates Schwann cells via the NMB receptor, inducing Schwann-cell reprogramming, promoting axon regeneration, and facilitating PNI by tumor cells.[111] Chronic stress activates sympathetic signaling in ovarian cancer, leading to elevated catecholamine levels, increased tumor burden, and enhanced invasive growth in mouse models; inhibition of β-adrenergic signaling can suppress tumor progression.[112] Neuropeptide FF promotes epithelial ovarian cancer cell invasion by upregulating matrix metalloproteinase-9 (MMP-9) expression via the ERK1/2 signaling pathway.[113] A Mendelian randomization study suggested that psychiatric disorders—including schizophrenia, bipolar disorder, major depressive disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder—may influence the risk of specific gynecologic cancers.[114]

In conclusion, the nervous system exerts complex and diverse effects on tumor progression. Although neural innervation predominantly promotes tumorigenesis, growth, and metastasis in most cases, it also demonstrates antitumor properties under certain conditions, highlighting the intricate regulatory role of the nervous system in cancer development. Further investigation into the nervous system's impact on various cancer types and the underlying mechanisms is essential for advancing cancer therapies. Table 1 summarizes the key molecules and signaling pathways through which the nervous system regulates tumor progression.

Mechanisms by which Nervous System Regulates Cancer

The nervous system regulates tumor initiation and progression through multiple mechanisms [Figure 2]. Neurons can form synapse-like structures with cancer cells, enabling direct electrical and chemical communication that activates malignant behaviors such as tumor cell proliferation and migration. In addition, the nervous system influences intercellular communication and signaling networks within the TME by secreting paracrine factors, including neurotransmitters and neurotrophic factors. Some cancer cells can also mimic neuronal functions by forming interconnected, neuron-like networks, which enhance their survival, migratory capacity, and resistance to therapy. Moreover, the gut microbiota–nervous system axis is being increasingly recognized for its role in modulating tumor immunity and cancer biology. The following sections will explore four major pathways through which the nervous system exerts its influence on cancer progression: neuron-cancer synapses, paracrine signaling,

Table 1: Key molecules and signaling pathways in the interaction between the nervous and tumors.

Diseases	Components in the nervous system	The impact of nervous system on cancer	Involved mechanism	References
OPG	Optic nerve	Stimulation of optic nerve activity increases optic glioma growth.	Germline Nf1 mutation in retinal neurons results in aberrantly increased shedding of NLGN3 within the optic nerve in response to retinal neuronal activity.	[9]
Glioma	Olfactory receptor neurons	Manipulating the activity of ORNs affects the development of glioma.	Olfaction excites M/T cells, which receive sensory information from ORNs and release IGF1 in an activity-dependent manner.	[11]
	Neuron	Glutamatergic synaptic input to glioma cells drives tumor progression.	Postsynaptic currents mediated by glutamate receptors of the AMPA subtype.	[115]
	Astrocytes	ADEVs hinder glioma growth.	ADEVs reduced both the expression and function of the volume-regulated anion channel.	[18]
GBM	Astrocytes	Astrocyte-derived CCL20 reinforces HIF-1-mediated hypoxic responses in GBM.	CCL20/CCR6 signaling pathway upregulates HIF-1α by stimulating nuclear factor kappa B-driven transactivation of the *HIF1A* gene.	[17]
Breast cancer	Sympathetic nerves	Artificial activation of CeM-CRH neurons and the CeM-CRH→LPGi circuit increased anxiety and tumor growth.	Manipulation of the CeM-CRH→LPGi circuit directly regulated the activity of the intratumoral sympathetic nerves and peripheral nerve-derived NE, which affected tumor progression by modulating anti-cancer immunity.	[116]
		Cell proliferation was increased by α2 -adrenoceptor action.	ERK 1/2 phosphorylation was mainly mediated by the PKA pathway.	[30]
		β2-adrenoceptor signaling regulates invadopodia formation to enhance tumor cell invasion.	β2-adrenoceptor signaling increased invasion of tumor cells from explanted primary tumors through surrounding extracellular matrix.	[32]
		Activation of β-AR drives proangiogenic factor production.	β-AR stimulation regulates VEGF production through the classical β-AR-cAMP-PKA pathway.	[35]
TNBC	Astrocytes	Interaction of tumor cells and astrocytes promotes breast cancer brain metastases.	Tumor cell-derived IL-1β and TNF-α increased the expression of TGF-β2 in astrocytes.	[39]
	Glutamatergic neurons	Synaptic proximity enables NMDAR signaling to promote brain metastasis.	Formation of pseudo-tripartite synapses between cancer cells and glutamatergic neurons, presenting a rationale for brain metastasis.	[40]
Prostate cancer	Sympathetic nerves	Autonomic nerve development contributes to prostate cancer progression.	Autonomic nerve fibers in the prostate gland regulate prostate cancer development and dissemination in mouse models.	[2]
	Sympathetic nerves	The activation of a sympathetic-FAK signaling pathway in prostate cancer patients with high degrees of depression facilitates tumor invasion.	FAK activation was dependent on a cAMP-PKA signaling pathway.	[52]
Pancreatic cancer	Sympathetic nerves	Interaction of the sympathetic nerve with pancreatic cancer cells promotes PNI through the activation of STAT3 signaling.	NE plays a critical role in pancreatic cancer PNI development and progression through the β-AR/PKA/STAT3 signaling pathway.	[61]
Pancreatic ductal adenocarcinoma	Sympathetic nerves	β2 adrenergic-neurotrophin feedforward loop promotes pancreatic cancer.	Atecholamines drive a feedforward loop, whereby upregulation of neurotrophins increases sympathetic innervation and local NE accumulation.	[57]
	Vagal nerve	Cholinergic signaling via muscarinic receptors suppresses pancreatic tumorigenesis.	CHRM1 inhibited downstream MAPK/EGFR and PI3K/AKT pathways in PDAC cells.	[64]
Gastric cancer	Parasympathetic nerve	Nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling.	Cholinergic stimulation of the NGF expression, and in turn NGF overexpression within gastric epithelium expanded enteric nerves and promoted carcinogenesis.	[117]
	Parasympathetic nerve	Acetylcholine acts through M3 muscarinic receptor to activate the EGFR signaling and promotes gastric cancer cell proliferation.	ACh, via M3R, activated the EGFR signaling to induce the phosphorylation of ERK1/2 and AKT.	[72]
Ovarian cancer	Brain-derived neurotrophic factor	BDNF/TrkB pathway enhanced cancer cell migration and invasion.	BDNF, the TrkB ligand, induced activation of TrkB in a dose dependent manner.	[118]

ACh: Acetylcholine; ADEVs: Astrocyte-derived extracellular vesicles; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AKT: Protein kinase B; BDNF: Brain-derived neurotrophic factor; CeM: Central medial; CHRM1: Cholinergic receptor muscarinic 1; CRH: Corticotropin-releasing hormone; EGFR: Epidermal growth factor receptor; FAK: Focal adhesion kinase; GBM: Glioblastoma; HIF: Hypoxia-inducible factor; IGF1: Insulin-like growth factor 1; MAPK: Mitogen-activated protein kinase; M/T: Mitral and tufted; NGF: Nerve growth factor; NLGN3: Neuroligin 3; NMDAR: N-methyl-D-aspartate receptor; OPG: Optic pathway glioma; ORNs: Olfactory receptor neurons; PDAC: Pancreatic ductal adenocarcinoma; PNI: Perineural invasion; TNBC: Triple-negative breast cancer; STAT3: Signal transducer and activator of transcription 3.

neuron-like tumor networks, and the microbiota–nervous system axis.

Neuron–cancer synapses

Advanced imaging and electrophysiological studies have confirmed the presence of functional chemical synapses between presynaptic neurons and postsynaptic GBM cells.[119] Tumors exploit these neuron–cancer synapses by expressing synapse-related proteins, fostering neural–tumor crosstalk that promotes malignancy.[115,119,120] In gliomas, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors at neuron–glioma synapses influence calcium signaling, stimulating tumor cell

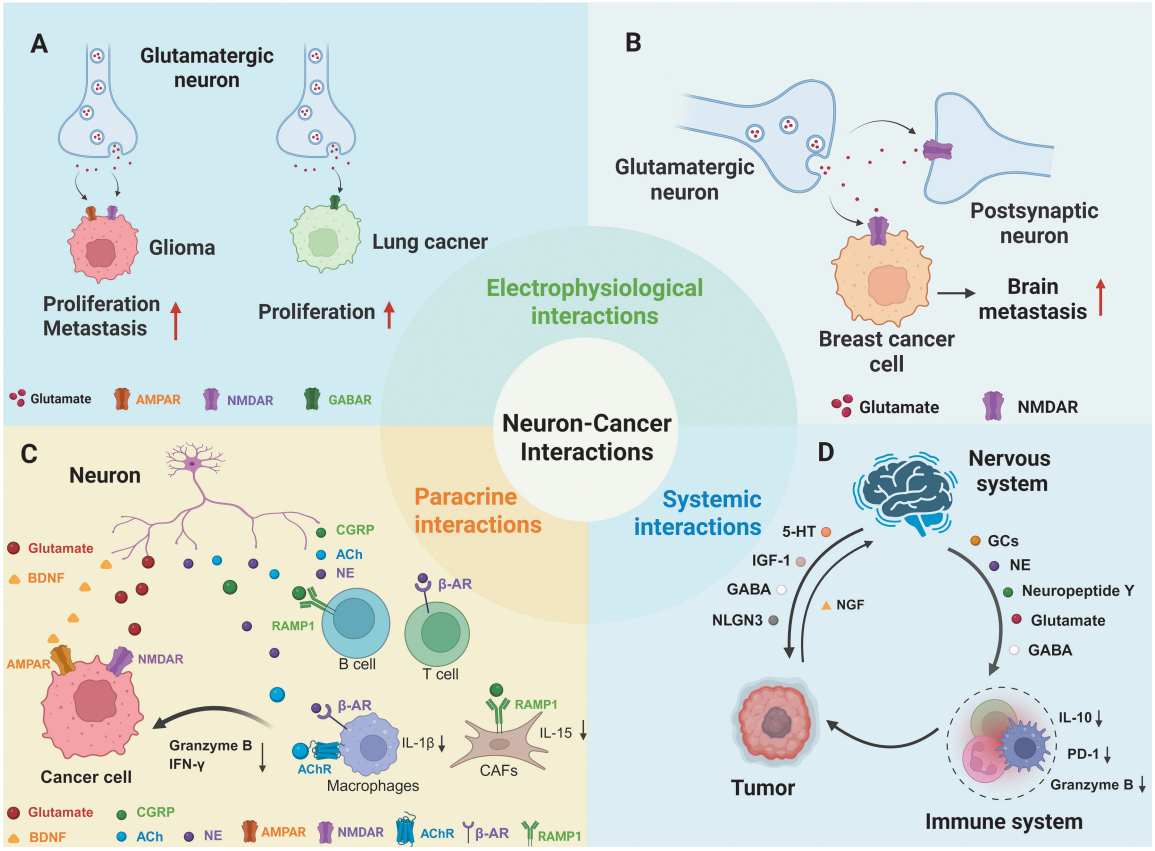

Figure 2: Crosstalk between the nervous system and tumors. (A) Glutamatergic neuron–tumor synapses promote tumor cell proliferation and metastasis. (B) Pseudo-tripartite synapses, where metastatic breast cancer cells replace astrocytes in the brain and form pseudo-tripartite synapses with glutamatergic synapses. (C) Paracrine interactions from neurons/nerves to cancer cells. For example, CGRP released by nociceptive neurons acts on RAMP1 expressed on B cells and CAFs, leading to reduced secretion of IL-15 and granzyme B. In addition, NE interacts with β-AR on macrophages and T cells, resulting in decreased IL-1β secretion and reduced IFN-γ production, thereby contributing to the formation of an immunosuppressive microenvironment. (D) Systemic interactions between the nervous system and cancer. The nervous system releases signaling molecules such as glucocorticoids, norepinephrine, neuropeptide Y, glutamate, and GABA, which act on the immune system and thereby influence tumor progression. Moreover, factors derived from the nervous system, including 5-HT, IGF-1, GABA, and NLGN3, can directly regulate tumor progression. Conversely, tumors can secrete NGF, which in turn feeds back to modulate the nervous system. ACh: Acetylcholine; AChR: Acetylcholine receptor; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF: Brain-derived neurotrophic factor; β-AR: β-adrenergic receptor; CAFs: Cancer-associated fibroblasts; CGRP: calcitonin gene-related peptide; GABA: Gamma-aminobutyric acid; GCs: Glucocorticoids; IFN-γ: Interferon-gamma; IGF-1: Insulin-like growth factor 1; IL-1β: Interleukin-1 beta; IL-10: Interleukin-10; IL-15: Interleukin-15; NE: Norepinephrine; NGF: Nerve growth factor; NLGN3: Neuroligin 3; NMDAR: N-methyl-D-aspartate receptor; PD-1: Programmed cell death protein 1; RAMP1: Receptor activity-modifying protein 1; 5-HT: 5-Hydroxytryptamine (serotonin).

networks and driving proliferation and invasion.[115,119] BDNF enhances GBM cell proliferation by increasing AMPA receptor activity on tumor cell membranes.[121] Furthermore, neuron–tumor synapses may facilitate GBM colonization in the brain.[122] SCLC forms tight contacts with neuronal glutamatergic terminals, which can evolve into genuine synapses. These synapses provide SCLC cells with glutamate input, conferring a significant proliferative advantage.[123] Tumor cells can also replace innervated tissues to form pseudo-tripartite synapses. For example, Zeng *et al*[40] demonstrated that breast cancer cells highly express N-methyl-d-aspartate receptor (NMDAR) after brain metastasis, displacing astrocytes and forming pseudotripartite synapses with glutamatergic neurons, thereby promoting metastatic cancer cell growth.

Neuron–cancer paracrine signaling interactions

The nervous system can also regulate tumor initiation and progression through the secretion of signaling molecules, including neurotransmitters, neurotrophic factors, and other signaling mediators.

For example, the autonomic nervous system secretes NE, E, and ACh, which influence tumor development. β-adrenergic signals from sympathetic nerves promote the initiation of prostate cancer,[3] and drive the progression of breast and ovarian cancers. In contrast, cholinergic signaling promotes gastric cancer,[73] but inhibits pancreatic cancer growth.[65] In a mouse model of pancreatic neuroendocrine tumors, glutamate activated NMDAR and its downstream signaling, promoting tumor growth and metastasis.[124] Similarly, the inhibitory neurotransmitter GABA promotes melanoma initiation and growth.[125] After being secreted by neurons, 5-HT enters ependymoma cells and binds to histone H3, a process that promotes tumor growth. Mechanistic studies have revealed that histone serotonylation in ependymoma increases the overexpression of the transcription factor ETS variant transcription factor 5, thereby facilitating tumor initiation and progression.[126]

Neuron activity-dependent paracrine signaling, such as the secretion of IGF1 and NLGN3 by neurons, along with certain neurotrophic factors, also regulates tumors. For

instance, olfactory neurons release IGF1 upon stimulation, promoting GBM formation in the olfactory bulb.[11] NLGN3 secreted by neurons and glial cells activates the PI3K-mammalian target of rapamycin (mTOR) pathway, driving GBM growth.[127,128] Neurotrophic factors also play crucial roles in tumor progression. Chronic stress, via β2-AR signaling, upregulates the secretion of NGF and BDNF, accelerating pancreatic cancer progression.[57] Cholinergic signaling increases NGF secretion in gastric cancer models, thereby promoting tumor progression.[117] In brain metastases of breast cancer, tumor-induced macrophages express glial cell-derived neurotrophic factor (GDNF), enhancing cancer cell survival.[129]

Neural-like cancer networks

Cancer cells can mimic the structure of the nervous system, forming interconnected, neural-like tumor networks. Astrocytes, for instance, form gap junctions via connexin 43, creating networks that support intercellular communication and resistance to oxidative stress.[130] Similarly, tumor cells establish tumor–tumor networks via gap junctions, enhancing tumor growth, metastasis, and resistance to anticancer treatments. These connections are primarily formed by long cellular extensions such as tumor microtubes (TMs) and tunneling nanotubes.[131,132] Preclinical studies have shown that GBM cells propagate Ca^{2+} waves through TM-connected networks, activating MAPK and nuclear factor kappa B (NF-κB) pathways to drive tumor growth.[133] Jung *et al*[134] found that the membrane protein Ttyh1 promotes TMs formation, significantly enhancing GBM growth and invasion. Remarkably, TMs may also help tumors repopulate resected cavities after surgical removal.[135] Moreover, tumor–tumor networks contribute to therapeutic resistance.[132,135] Inhibiting TMs can enhance the efficacy of chemotherapeutic agents such as TMZ and lomustine.[135,136]

Microbiota–nervous system axis

The gut microbiota–nervous system axis has attracted increasing attention in recent years for its role in cancer development and immune regulation. The gut microbiota can synthesize several neurotransmitters, such as 5-HT, GABA, glutamate, and dopamine. These signaling molecules can influence brain function and emotional states via pathways such as the vagus nerve and may also act directly on tumor cells, regulating their proliferation, migration, and invasiveness.[137,138] For example, glutamate can activate the STAT3 signaling pathway and upregulate the expression of the glutamate transporter GLAST on glioma cells, thereby indirectly enhancing their anti-apoptotic capacity and supporting tumor cell survival and expansion.[139]

In addition, microbial metabolites play a crucial role in modulating cancer progression. Studies have shown that isovalerate can induce tryptophan hydroxylase 2 expression, promoting 5-HT production and CRC initiation and metastasis.[140] Moreover, psychological stress significantly reduces the abundance of *Lactobacillus johnsonii* in the gut of CRC-bearing mice, disrupting microbial homeostasis and further accelerating tumor progression.[81]

Interactions Between the Nervous System and the TME

In addition to its direct effects, the nervous system also indirectly influences tumor progression by modulating immune responses and angiogenesis within the TME [Figure 3]. The TME, a complex ecosystem of cellular and noncellular components surrounding a tumor, plays a crucial role in tumorigenesis, progression, drug resistance, and metastasis.[141] The microbiota–nervous system axis also contributes to the regulation of host immune functions. Moreover, tumors can also actively induce intratumoral nerve growth via tumor neurogenesis, thereby increasing the nerve density.

Neuro–immuno–cancer crosstalk

The nervous system, immune system, and tumor cells form a complex network of three-way interactions that collectively regulate anti-tumor immunity. In pancreatic cancer tissues with low neural invasion, tertiary lymphoid structures composed of B cells, follicular helper T cells, and mature dendritic cells (DCs) are present. Additionally, cytotoxic T cells can become activated and migrate through the vasculature to the perineural regions, forming a defensive barrier and exhibiting characteristics of a "hot" tumor. In contrast, pancreatic tissues with high neural invasion display features of a "cold" tumor.[142] Astrocytes and microglia play a pivotal role in tumor progression by influencing the recruitment and function of immune cells. Immune cell transport and functionality are regulated by the SNS, which may impair anticancer immunity, whereas the parasympathetic nervous system may enhance anti-tumor immune responses. Furthermore, neurotransmitters such as GABA, glutamate, and 5-HT also significantly influence immune modulation, indicating the nervous system's capacity to reshape the TME through these intricate signaling interactions.[143]

In mouse brain metastasis models, lipocalin-2 induces the inflammatory activation of astrocytes, promoting the recruitment of immunosuppressive granulocytes to the brain metastasis microenvironment, thereby supporting melanoma and breast cancer metastasis.[92] Astrocytes also regulate the recruitment of tumor-associated macrophages (TAMs) through the expression of CCL2 and colony-stimulating factor (CSF1), facilitating GBM development.[144] Microglia increase anti-inflammatory factors through the mTOR-STAT3 signaling pathway while suppressing proinflammatory factors like NF-κB, thereby promoting immune evasion in GBM.[145] Co-culture experiments indicate that microglia increase immune suppressive molecules, such as IL-10 and PD-1, inhibiting T-cell proliferation and reducing the production of granzyme B and IFN-γ, thereby hindering anti-tumor immunity.[146–148]

The SNS can suppress anticancer immunity by regulating immune cell recruitment and function. Stress may activate the β2-AR-cAMP-FAK pathway in prostate cancer cells,

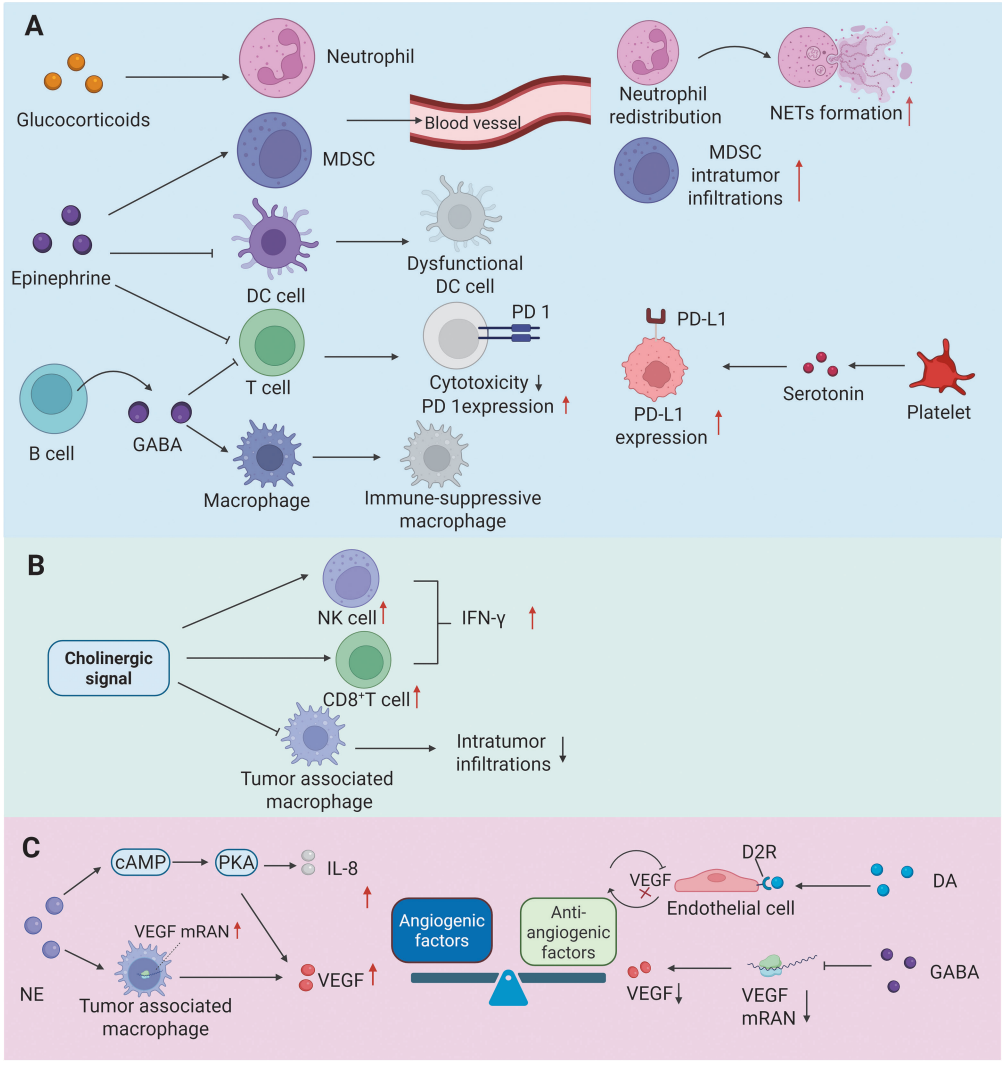

Figure 3: Influence of the nervous system on the TME, including regulation of the immune microenvironment and intratumor angiogenesis. (A) Inhibitory effects of the nervous system on the immune microenvironment. Glucocorticoids released during chronic stress increase neutrophil infiltration and neutrophil extracellular trap formation in the lung microenvironment, creating a favorable milieu for breast cancer metastasis. Adrenaline may promote the recruitment of MDSCs within tumors, leading to dysfunction of DCs and decreased effector cytokine expression by T cells, while simultaneously increasing PD-1 expression on T cells. GABA derived from B cells may inhibit T cell cytotoxicity and induce macrophages to adopt an immunosuppressive phenotype. Platelet-secreted 5-HT can enhance PD-L1 expression on both mouse and human cancer cells, diminishing the effector function of T cells within tumors. (B) Promoting effects of the nervous system on the immune microenvironment. Cholinergic signaling enhances the quantity and function of $CD8^+$ T cells and NK cells and inhibits the recruitment of TAMs. (C) The nervous system has a dual regulatory effect on angiogenesis within tumors. NE promotes the release of VEGF and IL-8 via the cAMP-PKA signaling pathway. Additionally, NE could enhance VEGF expression in TAMs, thereby increasing VEGF levels. These factors collectively enhance intratumoral angiogenesis. In endothelial cells, dopamine can inhibit intratumoral angiogenesis by inducing endocytosis of VEGFR2 through D2 dopamine receptors, preventing VEGF binding, receptor phosphorylation, and subsequent signaling. Furthermore, the inhibitory neurotransmitter GABA can suppress intratumoral angiogenesis by reducing VEGF expression. cAMP: Cyclic adenosine monophosphate; DA: Dopamine; DCs: Dendritic cells; D2R: Dopamine receptor D2; GABA: Gamma-aminobutyric acid; IFN-γ: Interferon-gamma; IL-8: Interleukin-8; MDSC: Myeloid-derived suppressor cell; mRNA: Messenger ribonucleic acid; NE: Norepinephrine; NK: Natural killer (cell); PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PKA: Protein kinase A; TAMs: Tumor-associated macrophages; TME: Tumor microenvironment; VEGF: Vascular endothelial growth factor; VEGFR2: Vascular endothelial growth factor receptor 2; 5-HT: 5-Hydroxytryptamine (serotonin).

leading to the release of neuropeptide Y and the subsequent recruitment of MDSCs to the TME, promoting cancer cell proliferation.[149] Similarly, adrenaline can impair the metabolic function and induce exhaustion of $CD8^+$ T lymphocytes, leading to immune suppression.[150,151] In B-cell lymphoma, β-AR signaling suppresses $CD8^+$ T-cell proliferation and reduces IFN-γ production, weakening their response to immunotherapy.[152] SNS activation also upregulates Tsc22d3 in DC, blocking type I IFN response and diminishing the efficacy of PD-1-targeted immunotherapies.[153] Additionally, chronic stress-induced SNS activation in mice results in reduced T-cell infiltration and increased neutrophil infiltration in the lung microenvironment, creating a favorable niche for breast cancer metastasis.[24]

However, emerging evidence suggests that SNS has a context-dependent role in cancer, and may also be protective under certain conditions. For example, activation of the brain reward system in tumor-bearing mice reduces noradrenergic signaling, thereby diminishing the immunosuppressive activity of MDSCs and slowing tumor growth.[154] Similarly, mice housed in enriched environments exhibited enhanced NK-cell infiltration and cytotoxicity against tumors, an effect dependent on β-adrenergic signaling.[63] In pancreatic cancer models,

sympathetic denervation accelerated tumor growth and was associated with increased infiltration of $CD163^+$ macrophages, indicating that SNS innervation can restrain tumor progression in specific contexts.[62] These findings highlight the dual role of SNS in cancer, which can either promote or inhibit tumor progression depending on neural activity, immune context, and tumor type.

Conversely, the parasympathetic nervous system may enhance anticancer immunity. In pancreatic cancer, cholinergic signaling inhibits the recruitment of TAMs, thereby suppressing tumor growth.[65] In breast cancer mouse models, electroacupuncture stimulation of the vagus nerve significantly reduced proinflammatory cytokines (such as IL-1β and TNF-α) in the serum and tumors, and increased $CD8^+$ T cells and NK cells, thereby enhancing anti-tumor immunity.[45] Conversely, vagotomy promotes tumor growth through inflammation and the recruitment of TAMs.[64]

Beyond the autonomic nervous system, other neural signals also play critical roles in modulating the anticancer immune response. Neurotransmitters such as GABA, glutamate, 5-HT, glucocorticoids, and sensory neurons contribute to this process. GABA downregulates the expression of chemokines CCL4 and CCL5 in CRC, inhibiting DC antigen presentation and reducing $CD8^+$ T-cell infiltration within the tumor.[155] GABA derived from B-cells promotes the differentiation of monocytes into anti-inflammatory macrophages that secrete IL-10, suppressing the cytotoxic function of $CD8^+$ T cells.[156] Under hypoxic conditions, glioma cells secrete high levels of glutamate, the principal excitatory neurotransmitter in the brain. It activates local neurons and promotes microglial M2 polarization through miR-200c-3p-enriched exosomes, driving glioma progression.[157] Li *et al*[158] found that overexpression of CNS-enriched N-acetyltransferase 8-like (NAT8L) and its metabolite N-acetylaspartate in drug-resistant tumors may suppress NK and $CD8^+$ T-cell cytotoxicity, weakening their anti-tumor activity. 5-HT may also play an immunosuppressive role by enhancing PD-L1 expression on platelets, thereby reducing the efficacy of $CD8^+$ T cells.[159] Sensory neurons can modulate anti-tumor immunity by releasing CGRP, suppressing the effector function of $CD8^+$ T cells in mouse melanoma models.[160]

Interactions between the microbiota–nervous system axis and the immune system

The gut microbiota plays a pivotal role in regulating the tumor immune microenvironment by releasing metabolic products and modulating autonomic nervous system activity.[137,161] The microbiota–nervous system–immune system axis exerts dynamic, stage-dependent effects on tumor immunoregulation throughout cancer progression. In the early stages, microbiota-derived neurotransmitters—such as 5-HT and dopamine—directly activate local immune surveillance. Tryptophan absorbed in the small intestine can be metabolized by gut bacteria into indole derivatives, thereby participating in immune regulation.[162,163] Dysbiosis-generated metabolic byproducts, including toxins and cytokines, may induce inflammation and promote CRC initiation and progression, indicating that a healthy gut microbiota may exert tumor-suppressive effects.[164,165] Meanwhile, strengthening antitumor immunity through vagal pathways can further inhibit tumor growth.[166,167] Conversely, the nervous system can also regulate gut microbiota homeostasis, thereby influencing the host's immune status.[137,161]

As tumors progress to advanced stages, psychological stress can suppress the secretion of Brunner's glands in mice via the vagus nerve, leading to reduced lactic acid bacteria in the gut and compromised immune function.[168] Gut microbiota dysregulation caused by GBM can also modulate the efficacy of immunotherapy. Dietary tryptophan supplementation restores the stability of the *Duncaniella dubosii*-associated microbial community and significantly enhances immunotherapy responses by promoting T-cell circulation.[169] In addition, stress-induced proinflammatory cytokines and neuroendocrine factors—such as catecholamines, histamine, 5-HT, and corticotropin-releasing hormone (CRH)—can disrupt the gut–brain axis, disturb microbiota homeostasis, and impair the function of NK cells and T cells, thereby accelerating tumor progression.[170,171] Notably, stress-related dysbiosis of the gut microbiota can reduce the abundance of bacteria responsible for producing SCFAs, which are crucial for the development and maintenance of $CD8^+$ memory T cells.[172,173] In patients with solid tumors, the efficacy of PD-1-targeted immune checkpoint inhibitors has also been positively correlated with SCFA levels.[174] Moreover, SCFAs produced by the gut microbiota can stimulate enterochromaffin cells in the intestinal epithelium to secrete 5-HT. Excessive 5-HT not only suppresses $CD8^+$ T cell infiltration and effector functions but also induces PD-L1 expression, thereby promoting the progression of pancreatic cancer and CRC.[171]

Overall, the regulatory pattern of this axis shifts from early immune activation to late immune suppression. Changes in microbial composition (from commensal dominance to pathogen enrichment) and alterations in neural regulatory patterns (from cholinergic anti-inflammatory to sympathetic proinflammatory activity) constitute the core mechanisms underlying this transition.

Neural regulation of angiogenesis

The nervous system also regulates angiogenesis within tumors. Catecholamines, including adrenaline and noradrenaline, released by the SNS, act on tumor cells to activate the cAMP-PKA signaling pathway, inducing the release of VEGF and IL-8, thereby promoting angiogenesis.[112,175] β2-adrenergic signaling can enhance angiogenesis by inhibiting endothelial cell oxidative phosphorylation, thereby driving cancer progression.[51] The parasympathetic agonist carbachol also stimulates VEGF-A production and angiogenesis by activating muscarinic receptors.[176] Therapeutic strategies targeting neural regulation of angiogenesis have shown potential. For instance, β2-AR knockout or inhibition can prevent neovascularization and suppress cancer progression.[51] However, certain neural regulatory pathways can inhibit tumor angiogenesis. Dopamine, through D2 receptors, induces the internalization of VEGF receptor

2, preventing vascular permeability factor (VPF)/VEGF binding and signaling, thereby inhibiting tumor angiogenesis.[177] The inhibitory neurotransmitter GABA also reduces VEGF expression and inhibits cholangiocarcinoma angiogenesis.[178]

Cancer-induced neural remodeling and neoaxonogenesis

Neoaxonogenesis refers to the process by which newly formed nerve axons grow toward and extend into the tumor. Cancer cells can express neurotrophic markers such as NGF, BDNF, and release exosomes to induce neoaxonogenesis.[179,180] For instance, PDAC can reprogram neuronal processes including calcium signaling, synaptogenesis, and microtubule organization—features characteristic of axon sprouting.[181] NGF produced by PDAC increases intratumoral nerve density and accelerates tumor progression.[57] Pancreatic cancer cells secrete neurotrophic factors that act on Trk receptors in nerves to promote neuronal survival and axon growth, mediating neural–cancer crosstalk within the TME.[182] Under catecholamine stimulation, tumor cells produce elevated BDNF, which signals through host neurotrophic receptor tyrosine kinase 2 in the TME, enhancing tumor innervation.[183] Exosomes released by patient-derived tumors can induce neurite outgrowth in PC12 cells. Inhibition of exosome release leads to a reduction in tumor innervation.[184]

Enhanced tumor innervation, in turn, promotes cancer cell proliferation and upregulates the production of neurotrophic factors by tumor cells, potentially establishing a positive feedback loop that further accelerates tumor growth.[2]

Impact of Cancer and Anticancer Treatments on the Nervous System

The communication between the nervous system and tumors is bidirectional. Tumor cells can reshape neural circuits, leading to neural hyperexcitability and various complications. Cancer treatments can also cause neurological side effects, impacting sensory, motor, cognitive, and autonomic functions. Therefore, understanding these effects is crucial for optimizing treatment strategies and improving patients' quality of life. Supplementary Figure 2, http://links.lww.com/CM9/C916 illustrates the impact of cancer and its treatments on the nervous system.

Impact of tumors on the nervous system

Tumor cells can disrupt normal neural function. Electroencephalograms show increased neuronal excitability in patients with gliomas, suggesting that gliomas may enhance neuronal excitation;[185,186] this hyperexcitability may contribute to tumor-related seizures.[185,187,188] In GBM mouse models, microglial infiltration begins before seizure onset, and seizure frequency increases with tumor progression.[189] In glioma models, the reduction of GABAergic inhibitory neurons leads to excessive excitation of the neural network around the tumor, promoting seizure activity.[190] In patients with GBM with seizures, the aberrant overexpression of potassium channels disrupts ionic homeostasis between the tumor and neurons, enhancing the excitability of peripheral tumor-associated neurons.[191] Gliomas can also remodel functional neural circuits, thereby promoting tumor development and impairing cognitive function.[192] For example, gliomas secrete factors like glutamate and synaptic proteins (such as phosphatidylinositol-3 and thrombospondin-1), which reshape neural circuits, increase neural activity, and ultimately affect tumor progression.[2]

Cancer can also influence physiological rhythms and induce pain by altering neuronal activity. In non-metastatic breast cancer mouse models, cancer induction led to abnormal activity in lateral hypothalamic hypocretin/orexin neurons, disrupting sleep patterns and altering metabolism.[193] In various mouse tumor models, cancer cells secrete chemotactic factors or angiogenesis (such as VEGFs), which invade peripheral nerves, increase pain sensitivity, and contribute to cancer-related pain.[194,195] Furthermore, cancer cells can disseminate along neural pathways. In prostate cancer mouse models, cancer cells promote peripheral nerve invasion through neural signaling, increasing neural innervation in the local TME.[196] Pancreatic cancer may also activate Schwann cells, promoting migration and invasion along nerves.[197]

Impact of anticancer treatment on the nervous system

In addition to the direct effects of cancer, cancer treatments can have adverse effects on the nervous system. Radiotherapy and chemotherapy can directly damage the CNS and lead to cognitive dysfunction, manifesting as deficits in attention, memory, and executive functions.[198,199] These treatments may harm CNS tissues, particularly white matter, and reduce hippocampal volume.[200,201] Parihar and Limoli[202] demonstrated that brain irradiation significantly reduces the number and density of dendritic spines in the dentate gyrus, leading to neurocognitive impairment. Additionally, cancer therapies may disrupt brain network connectivity, resulting in cognitive impairment.[203,204] Chemotherapeutic agents, such as doxorubicin, methotrexate, and 5-FU, cause cognitive dysfunction, which is referred to as "chemobrain".[205,206]

Cancer treatments can also lead to peripheral neuropathy, resulting in sensory, motor, and autonomic dysfunction, as well as neuropathic pain.[207] For example, patients with breast and lung cancer receiving radiotherapy may develop brachial plexopathy, characterized by sensory abnormalities or delayed reflexes.[208] Both radiotherapy and chemotherapy can also induce motor dysfunction, affecting balance, coordination, and upper limb function.[209–211] Moreover, pediatric patients with cancer often face endocrine complications due to treatment, including growth hormone deficiency, central precocious puberty, and adrenocorticotropic hormone deficiency.[212] Furthermore, cancer immunotherapy may also cause neurological damage.[213,214] However, the specific mechanisms remain incompletely understood and may be related to excessive immune activation, leading to autoimmune responses in the host.[215]

Neural Modulation of Cancer Treatments and Therapeutic Opportunities

The interactions between the nervous system and tumors not only promote malignant behavior and disease progression but may also compromise the efficacy of standard cancer treatments such as radiotherapy, chemotherapy, surgery, and immunotherapy.[216] Novel cancer treatment strategies targeting neurobiology—through pharmacological or nonpharmacological interventions—suppress the progression of certain tumors. Integrating these strategies with standard therapies may help delay tumor growth and improve patients' quality of life. Figure 4 illustrates these strategies, including both pharmacological and non-pharmacological approaches that disrupt the connections between nerves and tumors, serving as a beneficial complement to existing therapies.

Neural innervation impairs cancer therapies

As previously mentioned, neural innervation promotes the progression of various cancer types, including breast, prostate, and pancreatic cancers. Moreover, accumulating evidence suggests that neural regulatory mechanisms may also impair the efficacy of standard anticancer therapies, such as chemotherapy, radiotherapy, and immunotherapy.

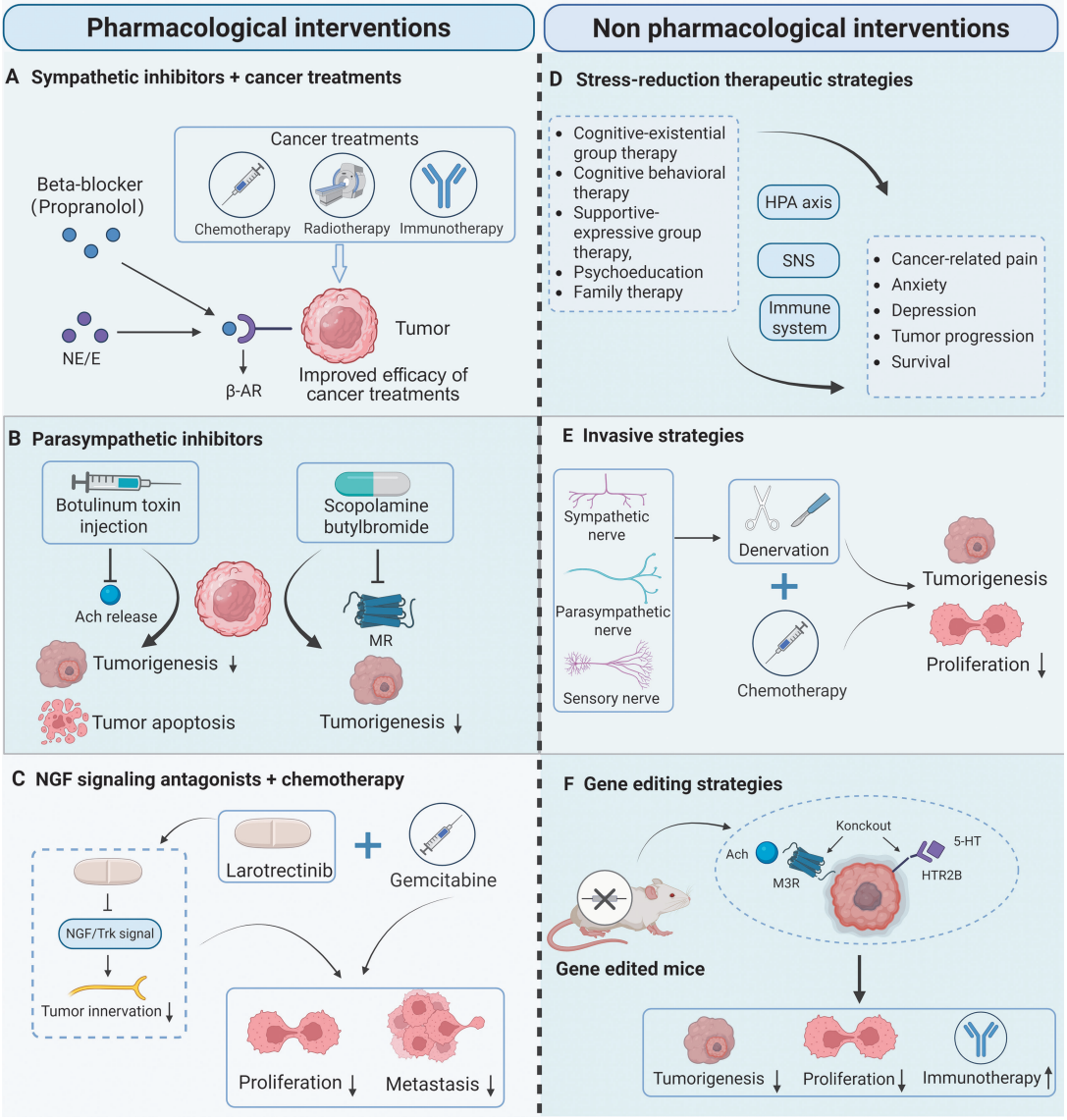

Figure 4: Neuron–cancer interfaces as a new avenue for cancer therapy development. Pharmacological interventions. (A) SNS inhibitors, such as propranolol, can suppress sympathetic signaling, thereby enhancing the efficacy of chemotherapy, radiotherapy, and immunotherapy in cancer treatment. (B) Parasympathetic nervous system inhibitors, such as botulinum toxin, can inhibit the release of ACh, reduce tumor progression, and promote tumor cell apoptosis. Scopolamine butylbromide can block muscarinic receptors, thereby suppressing tumor initiation. (C) Larotrectinib, by inhibiting the NGF/Trk signaling pathway, reduces tumor innervation and enhances the effectiveness of gemcitabine chemotherapy, resulting in decreased tumor proliferation and metastasis. Nonpharmacological interventions. (D) Stress-reduction psychological interventions, by modulating the HPA axis, SNS, and immune system, can alleviate cancer-related pain, depression, and anxiety, while also suppressing or delaying tumor progression and extending patient survival. (E) Surgical denervation combined with chemotherapy can inhibit tumor initiation and proliferation. (F) Gene-editing strategies, such as knockout of *M3R* or *HTR2B*, can reduce tumor initiation and growth and improve immunotherapy efficacy. ACh: Acetylcholine; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; β-AR: β-adrenergic receptor; Cx43: Connexin 43; NE: Norepinephrine; NGF: Nerve growth factor; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; SNS: Sympathetic nervous system; TM: Tumor microtubule; TNBC: Triple-negative breast cancer; TrkA: Tropomyosin receptor kinase A.

Chemotherapy

Sympathetic neural signaling not only promotes tumor progression but may also contribute to reduced chemotherapy efficacy. In ovarian cancer, for instance, NE signaling diminishes chemosensitivity.[217] Chronic stress can enhance cancer cell adhesion to the ECM, induce resistance to cisplatin and paclitaxel,[218] and significantly reduce the efficacy of oxaliplatin.[153] In cervical cancer cells, both NE and E reduce the therapeutic efficacy of doxorubicin by activating β2-ARs, thereby inhibiting doxorubicin-induced acetylation of p53.[110] Hara *et al*[219] further proposed that this chemotherapy resistance may be mediated by neurotransmitter-induced downregulation of p53 expression, which in turn increases genomic instability in cancer cells.

Moreover, certain chemotherapeutic agents may themselves enhance tumor sensitivity to sympathetic neural signaling. Studies have shown that anthracyclines, such as doxorubicin, can upregulate β2-AR expression in breast cancer cells, thereby increasing tumor responsiveness to subsequent neurotransmitter signals and potentially exacerbating adverse effects on future treatments.[220]

Radiotherapy

Enhanced sympathetic nervous activity can increase tumor resistance to radiotherapy. Sympathetic signaling may regulate intracellular stress responses and DNA repair mechanisms, reducing the sensitivity of tumor cells to radiation-induced cytotoxicity.[221] In contrast, blocking sympathetic signaling can enhance tumor-specific T cell activity and antigen-specific immune responses, thereby augmenting the antitumor effects induced by radiotherapy.[151] In GBM, tumor cells rely on "neuron–tumor network connectivity" for signal integration and survival support, which contributes to their increased resistance to conventional radiotherapy.[222]

Immunotherapy

Sympathetic signaling exerts multiple immunosuppressive effects through β2-AR, thereby impairing the efficacy of immunotherapy. Studies have shown that activated β2-AR suppresses $CD8^+$ T cells cytotoxicity and promotes the accumulation of MDSCs and regulatory T cells, collectively weakening the overall antitumor immune response.[4,223] In the context of immunotherapy, stress-associated neural activation may lead to decreased cytotoxic T lymphocyte numbers, increased regulatory T cell infiltration, and reduced $CD8^+$ T-cell density within tumors, ultimately impairing the effectiveness of anti-PD-L1 therapies.[224,225]

Targeting neurobiology to enhance therapeutic efficacy

As the role of the nervous system in regulating tumor initiation and progression becomes increasingly understood, neuroregulation-based antitumor strategies have rapidly emerged. Table 2 summarizes key therapeutic strategies based on neuro–tumor interactions. Among various interventions, targeting sympathetic, parasympathetic, and other neurotransmitter signaling pathways through pharmacological or non-pharmacological approaches has shown promising efficacy in multiple tumor models and clinical studies. Moreover, these interventions have demonstrated the potential to enhance the effectiveness of conventional therapies such as chemotherapy, radiotherapy, and immunotherapy, offering new opportunities for integrated cancer treatment.

Pharmacological interventions

Sympathetic inhibitors

Sympathetic signaling inhibitors primarily function by blocking the binding of E and NE to adrenergic receptors, thereby suppressing the activity of the sympathetic-adrenal system. These agents are commonly used in treating hypertension, angina pectoris, arrhythmias, anxiety, and other conditions.[226] Among them, β-AR blockers (β-blockers), such as propranolol and atenolol, have garnered increasing attention in the field of oncology. Numerous retrospective studies have demonstrated that β-blockers may inhibit the progression of various solid tumors, including melanoma, breast cancer, ovarian cancer, CRC, prostate cancer, pancreatic cancer, and lung cancer, and may contribute to improved patient survival.[227–229]

In addition to direct antitumor effects, inhibiting sympathetic signaling enhances the efficacy of standard cancer therapies. Anthracycline-based chemotherapeutic agents are known to activate sympathetic activity and alter the TME; co-administration of β-blockers may therefore potentiate their therapeutic effects.[230] Supporting this, Kokolus *et al*[231] reported that propranolol improved the response to immunotherapy in a murine melanoma model.

Moreover, propranolol in combination with dichloroacetate enhances the effects of chemoradiotherapy and significantly increases the sensitivity of head and neck squamous cell carcinoma to cisplatin and radiation in both *in vitro* and *in vivo* settings.[232] Propranolol also augments the antitumor efficacy of radiotherapy in a CT26 murine colorectal adenocarcinoma model.[221]

Beyond chemotherapy and radiotherapy, β-blockers may exert synergistic effects in immunotherapy. For example, atenolol blocks β-ARs and prevents T-cell exhaustion, thereby enhancing T-cell functionality.[233] β-blockers can also alleviate the suppressive impact of adrenergic stress on the efficacy of combined PD-L1 immune checkpoint blockade and radiotherapy, ultimately improving antitumor immune responses.[151]

Parasympathetic inhibitors

Botulinum toxin inhibits the release of ACh at the terminals of motor and parasympathetic nerves, thereby blocking neural signal transmission. Its antitumor effects have been preliminarily validated in various animal models and human studies; botulinum toxin injections

Table 2: Treatment strategies based on neuron–cancer interactions.

Diseases	Treatment	Therapeutic target (neuro–tumor/tumor–tumor)	Involved mechanism	References
Glioma	Anaesthesia or perampanel	Neuro-tumor	Perampanel inhibits synchronized calcium transients in tumor-microtube-connected glioma networks, reducing tumor invasion and growth.	[119,115]
	Perampanel	Neuro-tumor	Perampanel, a novel AMPA receptor antagonist, works by inhibiting the AMPA receptors to prevent seizures and tumor progression in glioma patients.	[287]
	αCT1 (selective inhibitor of Cx43 channels)	Tumor-tumor	Combining a Cx43 inhibitor with TMZ could enhance therapeutic responses in GBM.	[288]
GBM	Meclofenamate	Tumor-tumor	Inhibition of intercellular cytosolic trafficking via gap junction augments lomustine-induced toxicity in GBM.	[136]
	Meclofenamate	Tumor-tumor	MFA effectively dismantles both the functional and morphological aspects of TM-based syncytial network architectures, thereby enhancing TMZ therapeutic responses in GBM.	[289]
Astrocytomas	sh *Cx43*	Tumor-tumor	Disconnection of astrocytoma cells by targeting their TMs emerges as a new principle to reduce the treatment resistance.	[135,132]
Breast cancer	Propranolol	Neuro-tumor	The immunosuppressive function of MDSCs can be mitigated by treatment with β-AR antagonists.	[290]
		Neuro-tumor	Inhibiting β2-adrenergic signaling in the TME enhances the therapeutic efficacy of anthracycline chemotherapy by reducing metastasis in xenograft mouse models.	[230]
		Neuro-tumor	β-antagonist propranolol reversed the stress-induced macrophage infiltration and inhibited tumor spread to distant tissues.	[34]
Gastric cancer	Disrupting the vagus nerve trunk or local injection of type A botulinum toxin	Neuro-tumor	Denervation-induced suppression of tumorigenesis was associated with inhibition of Wnt signaling and suppression of stem cell expansion.	[73]
	4-DAMP (M3R antagonist)	Neuro-tumor	ACh could act through M3R and the EGFR signaling to promote gastric cancer cells proliferation, targeting M3R or EGFR may provide us a potential therapeutic strategy for gastric cancer treatment.	[72]
Pancreatic cancer	Activate the sympathetic nerves	Neuro-tumor	Exposure to enriched environment enhanced NK cell activity against tumors and promoted tumoral infiltration of NK cells.	[63]
	Propranolol	Neuro-tumor	Stress-induced neural activation increased primary tumor growth and tumor cell dissemination to the normal adjacent pancreas. These effects could be reversed by β-blockade.	[282]
PDAC	Ablation of sensory neurons	Neuro-tumor	Sensory neuron ablation by neonatal capsaicin injection prevented PNI.	[70]
	Bethanechol	Neuro-tumor	Systemic administration of a muscarinic agonist suppresses tumorigenesis through MAPK and PI3K/AKT signaling.	[64]
Pancreatic cancer and CRC	Fluoxetine or telotristat	Neuro-tumor	Depletion of 5-HT cargo or inhibition of 5-HT release from thrombocytes decreased growth of syngeneic pancreatic and colorectal tumors in wild-type mice, increased $CD8^+$T cell influx, and decreased PD-L1 expression.	[159]
Cholangiocarcinoma	GABA	Neuro-tumor	GABA inhibited cancer cell migration and, significantly decreased tumor volume, tumor cell proliferation, and VEGF-A/C expression whereas increasing apoptosis.	[178]
Prostate cancer	Propranolol	Neuro-tumor	NE induces neuroendocrine differentiation-like changes in prostate cancer cells, and NE-mediated neuroendocrine differentiation is effectively inhibited by the β2-AR blocker propranolol.	[53]
	6-hydroxydopamine	Neuro-tumor	The early phases of tumor development were prevented by chemical or surgical sympathectomy and by genetic deletion of stromal β2- and β3-adrenergic receptors.	[2]
	Scopolamine	Neuro-tumor	Cholinergic-induced tumor invasion and metastasis were inhibited by pharmacological blockade or genetic disruption of the stromal type 1 muscarinic receptor, leading to improved survival of the mice.	[2]
Melanoma	Picrotoxin (GABA-A receptor antagonist)	Neuro-tumor	GABAergic signaling across the skin microenvironment regulates the ability of oncogenes to initiate melanoma.	[125]
	Propranolol	Neuro-tumor	β-AR blockade enhances the control of murine melanoma growth by anti-(α) PD-1 checkpoint blockade.	[231]

ACh: Acetylcholine; AKT: Protein kinase B; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AR: Adrenergic receptor; β2-AR: β2-adrenergic receptor; CRC: Colorectal cancer; Cx43: Connexin 43; EGFR: Epidermal growth factor receptor; GABA: Gamma-aminobutyric acid; GBM: Glioblastoma; M3R: Muscarinic acetylcholine receptor 3; MAPK: Mitogen-activated protein kinase; MDSCs: Myeloid-derived suppressor cells; MFA: Meclofenamate; NE: Norepinephrine; NK cell: Natural killer cell; PDAC: Pancreatic ductal adenocarcinoma; PD-1: Programmed cell death protein 1; PI3K: Phosphoinositide 3-kinase; PNI: Perineural invasion; TM: Tumor microtubule; TME: Tumor microenvironment; TMZ: Temozolomide; VEGF: Vascular endothelial growth factor; 5-HT: 5-Hydroxytryptamine (serotonin); 4-DAMP: 4-Diphenylacetoxy-N-methylpiperidine methiodide.

significantly suppress gastric tumor formation in mice and reduce tumor volume while promoting apoptosis in pancreatic cancer models using athymic nude mice.[73,234] Additionally, scopolamine butylbromide, a parasympatholytic agent, effectively reduces the incidence of intestinal tumors in mouse models, suggesting that parasympathetic signaling pathways may play a role in tumor initiation and progression.[235]

NGF signaling antagonists

NGF promotes the generation of new axons and facilitates neural infiltration into tumor tissues. In breast and pancreatic cancer, both systemic and local administration of NGF receptor inhibitors or anti-NGF antibodies can effectively reduce neural density within tumor tissues and suppress tumor growth.[57,236] Zhang *et al*[237] further demonstrated that targeting NGF can inhibit neurogenesis in pancreatic cancer and exert antitumor effects.

Cholinergic stimulation in gastric epithelium can induce NGF expression, while NGF overexpression leads to intestinal nerve expansion and promotes tumorigenesis. Hayakawa *et al*[117] found that blocking NGF/Trk signaling significantly inhibits epithelial cell proliferation and tumor formation. NGF activates its receptor Trk, and larotrectinib is the first FDA-approved Trk inhibitor. It not only has potent antitumor activity in pancreatic cancer mouse models but also upregulates immune activation markers such as CD80 and CD86 in tumor tissues while suppressing the expression of CD206, indicating its potential in modulating the tumor immune microenvironment. When combined with gemcitabine, larotrectinib further enhances tumoricidal effects.[182]

Other neurotransmission-related agents

Clinical studies have shown that dopamine and its receptor DRD2 are highly expressed in GBM. DRD2 promotes tumor cell proliferation via the G protein subunit alpha i2 (GNAI2)/Rap1/Ras/ERK signaling pathway, and its antagonists can significantly inhibit tumor growth.[207] Furthermore, in mouse models, agents that inhibit the synthesis of GABA effectively prevent the development of melanoma, suggesting that the GABAergic pathway may play a critical role in tumorigenesis.[125]

Nonpharmacological interventions

Therapeutic strategies for stress reduction

Following a cancer diagnosis, patients often experience profound psychological distress and anxiety due to fear of death, loss of employment and income, diminished independence, and the negative impact of cancer and its treatment on daily functioning.[238,239] These psychological stressors may contribute to tumor progression. Therefore, stress-alleviating non-pharmacological therapeutic strategies have been increasingly integrated into cancer care and can enhance treatment efficacy when combined with conventional treatment.[229,240]

Psychological interventions were initially employed to relieve pain and emotional disorders in patients diagnosed with cancer. Common approaches include cognitive-existential group therapy, cognitive behavioral therapy, family therapy, supportive-expressive group therapy, and psychoeducation.[241,242] In patients with breast cancer, these interventions alleviate anxiety, depression, and pain symptoms, possibly by modulating stress-related sympathetic activation and the HPA axis, with reductions also reported in tumor recurrence and mortality rates.[243–247] In those with ovarian cancer, social support mitigates the suppressive effects of depression on the cytotoxic activity of NK cells and tumor-infiltrating lymphocytes.[248,249] Additionally, a 6-week structured psychosocial intervention in patients with melanoma enhanced coping abilities, reduced emotional distress, and was associated with delayed tumor recurrence and extended survival.[250]

Invasive strategies

Sensory innervation of the TME promotes tumor initiation and progression.[6] In a basal cell carcinoma mouse model, sensory nerve innervation activated the Hedgehog signaling pathway, which induces the proliferation of hair follicle stem cells and is essential for tumor development.[251] Ablation of these sensory nerves effectively suppressed tumor formation. Similarly, in pancreatic cancer models, ablation of sensory neurons delayed both tumor initiation and progression.[252] Beyond its cytotoxic properties, paclitaxel disrupts axonal transport in sensory nerves, reducing intratumoral nerve density by 62%. When combined with sympathetic denervation, the antitumor effect was enhanced by 16.5-fold.[181] Additionally, vagotomy in gastric cancer models suppressed Wnt signaling and reduced cancer stem cell expansion.[73]

Gene editing strategies

Targeting key molecules involved in neural signaling pathways has opened new avenues for cancer therapy. For instance, knockout of the M3 subtype of the acetylcholine (ACh) receptor significantly reduced the incidence of intestinal tumors in mice.[215] N-acetylaspartate, a metabolite enriched in the CNS, inhibited the formation of immunological synapses between NK/T cells and tumor cells, impairing cytotoxic function and contributing to immune resistance.[158] Targeting its biosynthetic enzyme NAT8L may help restore immunotherapy sensitivity in breast cancer. In addition, 5-HT and its receptor HTR2B are significantly upregulated in gastric adenocarcinoma tissues. In subcutaneous xenograft models, either genetic silencing of *HTR2B* or treatment with its antagonist SB204741 can significantly reduce tumor burden.[253]

Potential to redefine the cancer treatment paradigm

Unlike traditional "cytotoxic" therapeutic approaches, neural-targeted cancer therapy represents a fundamental shift in treatment philosophy. Rather than focusing solely on tumor cells, it operates from a systemic perspective of neural regulation, aiming to remodel the TME and restore organismal homeostasis.[4,254] First, targeting neural signaling pathways can potentially modulate multiple cancer-driving processes—including immune suppression, metabolic reprogramming, and angiogenesis—thereby enhancing the efficacy of existing immunotherapies and chemotherapies without increasing toxicity.[4,255,256] Second, research on neuro–tumor interactions has revealed a form of "co-evolution" between tumors and the host neural network, a concept that may catalyze a paradigm shift from "single-cell directed therapy" to "system-level regulatory therapy".[5,257] Looking ahead, integrated therapeutic

strategies combining neuromodulation, precision imaging, and artificial intelligence-based predictive modeling may enable the development of truly personalized neuro-oncology. Ultimately, successful clinical translation of therapies targeting neuro–tumor interactions depends on establishing a multidisciplinary, mechanism-driven, and standardized therapeutic framework with predictable outcomes. Only then can neural-targeted interventions progress from a potential adjuvant approach to a transformative breakthrough that can redefine the cancer treatment paradigm and bring new prospects for long-term survival and recovery.

Clinical studies support the feasibility of targeting neuro–tumor interactions as a potential anticancer strategy

In recent years, an increasing number of clinical studies have begun to explore the feasibility of targeting neuro–tumor interactions in cancer therapy. In Table 3, we have summarized the results of completed and published clinical trials targeting neuro–tumor interactions. Additionally, a large number of ongoing clinical trials are summarized in Table 4. Current evidence suggests that pharmacological modulation of neural signaling not only has good safety and tolerability but may also enhance antitumor immune responses, suppress tumor progression and metastasis, and provide new therapeutic strategies to improve patient survival. Among these, β-AR blocker propranolol has been extensively studied in clinical settings.

A phase II clinical trial showed that propranolol was well tolerated (with a 96% compliance rate) during neoadjuvant chemotherapy in patients with breast cancer, and no all-cause deaths occurred during treatment, confirming the safety and feasibility of propranolol in breast cancer therapy.[258] Furthermore, in patients with PDAC, preoperative administration of the muscarinic receptor agonist bethanechol significantly activated cholinergic pathways and reduced the expression of proinflammatory cytokines, further demonstrating the clinical potential of neuroregulation-based pharmacological interventions.[259]

Beyond safety, strategies targeting neuro–tumor interactions have also shown significant immune-enhancing effects. For instance, a phase I clinical trial evaluated the combination of propranolol and the PD-1 inhibitor pembrolizumab in patients with locally advanced or metastatic melanoma (NCT03384836). The results showed good treatment tolerance and an objective response rate of up to 78%. Post-treatment analysis revealed increased IFN-γ levels and decreased IL-6 levels, suggesting that the combination therapy may exert antitumor effects by reshaping the immune microenvironment.[260] In another study involving patients with CRC (NCT03245554), short-term propranolol intervention significantly increased $CD8^+$ T cell infiltration and granzyme B expression in tumor tissues, indicating an activating effect on T cell function.[261]

More importantly, existing clinical data suggest that nervous system modulation may also reduce the risk of distant metastasis and recurrence, thereby prolonging disease-free survival (DFS) and overall survival (OS). For example, in a study involving patients with TNBC, those treated with β-blockers had lower recurrence and metastasis rates and longer DFS compared to untreated patients.[262] In an Australian phase II randomized controlled trial, short-term preoperative use of propranolol significantly downregulated the expression of multiple metastasis-related molecular markers.[263] A large retrospective study of patients with lung cancer also found that β-blocker use was associated with significantly prolonged OS.[264] In a perioperative study on pancreatic cancer, propranolol combined with the cyclooxygenase-2 inhibitor etodolac extended median DFS from 11.25 to 16.36 months, and the incidence of distant metastasis decreased from 54.5% to 11.1%.[265]

Notably, several clinical trials have explored the combination of propranolol with other agents to enhance its regulatory effect on the tumor immune microenvironment. For example, in a clinical trial on early-stage breast cancer (NCT00502684), propranolol combined with the cyclooxygenase-2 inhibitor etodolac downregulated the proliferation marker Ki-67 and various pro-metastatic factors, while reducing tumor-infiltrating monocytes and increasing B cell infiltration, thereby suppressing disease recurrence.[262] Similarly, in a perioperative intervention study on CRC, combined propranolol and etodolac treatment significantly inhibited the EMT process and reduced the infiltration of $CD14^+$ monocytes and $CD19^+$ B cells in tumor tissues.[266] The 3-year recurrence rate was 12.5% (2/16) in the treatment group, compared to 33.3% (6/18) in the control group. These results suggest that combined intervention targeting neural signaling and inflammatory responses may further enhance the therapeutic efficacy of neuro–tumor regulation strategies.

However, some studies suggest that the efficacy of such interventions may vary depending on tumor type or treatment context. For instance, in a small-sample study, propranolol combined with chemotherapy did not improve progression-free survival (PFS: 7.79 months *vs*. 7.62 months, $P = 0.95$) or OS (21.2 months *vs*. 17.3 months, $P = 0.18$) in patients with ovarian cancer.[267] Similarly, retrospective analyses showed no significant association between β-blocker use and OS or mortality in prostate cancer.[268] Additionally, Zhou *et al*[269] examined 154 patients undergoing radical surgery for breast cancer and found that perioperative intervention with propranolol or parecoxib had no significant effect on the proportion of regulatory T cells, suggesting that the immunomodulatory effects may be time-sensitive or cancer-type specific.

Therapeutic strategies targeting nervous system regulation of tumor progression exhibit substantial variability in efficacy across different cancer types, largely due to three major sources of biological heterogeneity: the heterogeneous expression of neuronal receptors on tumor cells, the diverse modes of neural innervation of tumors, and tumor microenvironmental differences. First, tumor types display distinct expression profiles of neurotransmitter receptors. For example, the use of β-adrenergic blockers remodels the TME, increases T-cell infiltration, and reduces immunosuppressive cell populations,[270] and is associated with significantly improved recurrence-free survival (RFS) in patients with early-stage breast cancer.[271] However,

Table 3: Key completed clinical trials involving neuron-cancer interactions.

Clinical trial	Treatment	Patient characteristics	Outcomes	Enrollment (*n*)	Trial number
Study of propranolol to decrease gene expression of stress-mediated beta-adrenergic pathways in HCT recipients	Patients randomized to the Propranolol arm will be starting 7 days prior to transplant and continuing through 28 days post-transplant. Propranolol will start at 20 mg twice daily and will be titrated to 40 mg twice daily as tolerated.	18–75 years of age ≤1 year since initiation of systemic anti-myeloma therapy Patient is scheduled for autologous hematopoietic stem cell transplant as the upfront therapy for their multiple myeloma	Propranolol combined with transplant: (1) Lower anxiety and depression scores. (2) Faster neutrophil and platelet engraftment. (3) Reduced incidence of culture-positive infections and febrile neutropenia	25	NCT02420223
Perioperative administration of COX-2 inhibitors and beta blockers to women undergoing breast cancer surgery	Propranolol was administered orally: 20 mg of immediate release BID during the 5 days before surgery; 80 mg of extended release on the morning of surgery and on the evening and morning following surgery; 20 mg of immediate release BID thereafter during the five postoperative days.	Women that are scheduled to undergo surgery for a single, stage I–III, invasive ductal or lobular carcinoma tumor with curative intent No evidence of metastatic disease prior to surgery. Age between 20 and 70 years old.	Beta blockers combined with surgery: (1) Reducing tumor-infiltrating monocytes while increasing the number of tumor-infiltrating B cells; (2) Enhancing CD11a expression on circulating NK cells; preventing the perioperative decline in IL-12 and IFN-γ production; (3) Inhibiting multiple pathways associated with metastasis and recurrence breast cancer.	38	NCT00502684
The safety and efficiency of propranolol as an initial treatment for pediatric hemangioma	Patients received prednisolone (2 $mg \cdot kg^{-1} \cdot day^{-1}$) or propranolol (2 $mg \cdot kg^{-1} \cdot day^{-1}$) for 16 weeks	Hemangioma patient (0–9 months old) No treatment before 10%–20% volume increase in 2–4 weeks	(1) Propranolol reduction in hemangioma volume and ulceration area; (2) higher degree of epithelialization, cessation of proliferation, and vascular regression.	34	NCT01908972
β-adrenergic blocker and a COX-2 inhibitor for prevention of colorectal cancer recurrence	Participants received either the study drug or placebo for 20 consecutive days, beginning 5 days prior to tumor resection. Etodolac was administered orally at a dose of 400 mg twice daily. Propranolol was given orally, starting with 20 mg twice daily during the 5 days leading up to surgery. On the day of surgery, the dosage was increased to 80 mg twice. This was followed by 40 mg twice daily for the next 7 postoperative days, and then reduced to 20 mg twice daily for the final 7 days of treatment.	Patients planned for surgery for primary resection of colon and rectal cancer in curative intent. No evidence of metastatic disease prior to surgery. Age between 18 and 75 years old. ASA score of 1–3	Oral propranolol and etodolac combined with surgery: (1) Reduced tumor infiltrating CD14+monocytes and CD19+B cells. (2) Increased tumor-infiltrating CD56+NK cells.	34	NCT00888797
Effects of epidural anesthesia and analgesia on the prognosis in patients undergoing pancreatic cancer surgery	Lidocaine i.v. (continuous intraoperative infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$, after 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ bolus at induction of anesthesia) or saline placebo.	Undergoing elective pancreaticoduodenectomy for pancreatic cancer. 18 years to 80 years (adults).	Following intraoperative lidocaine infusion, circulating NETs were reduced, while tumor-associated NETs remained unchanged.	563	NCT03245346
INCB7839 in treating children with recurrent/progressive high-grade gliomas	Subjects received 120 $mg \cdot m^{-2} \cdot dose^{-1}$ of INCB7839 orally, twice a day for 28-day cycles.	Patients aged 3 -21 years with recurrent/progressive high-grade gliomas.	Progression-free survival rate was 18%, overall survival rate was 53.6%, and upregulation of ADAM10 enhanced the inhibition of HER2.	13	NCT04295759
The impact of intravenous anaesthesia on angiogenesis in patients with breast cancer	Experimental: Sevoflurane; Sevoflurane active comparator: sevoflurane + lidocaine; Experimental: Total intravenous anesthesia–target-controlled infusion (TIVA-TCI); Active comparator: TIVA-TCI + lidocaine	Patients aged 18 -80 years with breast cancer, ASA class I -III, and no metastatic disease were enrolled in the study.	TIVA-TCI: (1) Decreasing in neutrophil extracellular trapping and MMP3 (2) Decreasing tumor recurrence.	120	NCT02839668

(*continued*)

Table 3
(continued)

Clinical trial	Treatment	Patient characteristics	Outcomes	Enrollment (*n*)	Trial number
Clinical research on treatment of gastrointestinal cancer in the preoperative by propranolol	The participants who were treated with propranolol and placebo group for 1 week followed by surgical resection.	18–70 years old patients with gastric adenocarcinoma and colon cancer, who have been diagnosed without any prior treatment (including surgery or radiotherapy and chemotherapy) in the I–III period, no distant metastasis, suitable for patients with surgical resection of the tumor.	Propranolol treatment: (1) Higher frequency of intratumoral $CD8^+$ T cells. (2) Down-regulated the intratumoral level of phosphorylated ERK.	28	NCT03245554
Propranolol hydrochloride and pembrolizumab in treating patients with stage IIIC–IV melanoma that cannot be removed by surgery	Propranolol hydrochloride oral administration BID and pembrolizumab intravenous over 30 minutes of day 1. Courses repeat every 3 weeks for up to 2 years.	Participants must be newly diagnosed, treatment-naive with histologically confirmed stage IIIC unresectable melanoma or stage IV melanoma.	Propranolol hydrochloride combined with pembrolizumab: an increase in IFN-γ and a decrease in IL-6 were observed in responders.	47	NCT03384836
Donepezil in treating patients who have undergone radiation therapy for brain tumors	Weeks 1–6: One 5 mg oral tablet of donepezil hydrochloride or placebo tablet per day Weeks 7–24: Two 5 mg oral donepezil hydrochloride or placebo per day	Adults >18 years old. Life expectancy of at least >30 weeks. Must have received a prior course of at least 30 Gy fractionated whole or partial brain irradiation for treatment of a primary brain tumor or metastatic disease to the brain.	Donepezil treatment: Improved memory and language learning abilities (Hopkins Verbal Learning Test)	198	NCT00369785

ADAM10: A disintegrin and metalloproteinase 10; ASA score: American Society of Anesthesiologists physical status classification score; BID: Bis in die (twice daily); COX-2 inhibitors: Cyclooxygenase-2 inhibitors; HCT: Hematopoietic cell transplantation; HER2: Human epidermal growth factor receptor 2; IFN-γ: Interferon-gamma; IL-6: Interleukin-6; IL-12: Interleukin-12; MMP3: Matrix metalloproteinase 3; NETs: Neutrophil extracellular traps; NK cells: Natural killer cells; TIVA-TCI: Total intravenous anesthesia–target-controlled infusion.

studies on ovarian cancer have demonstrated no significant association between perioperative β-blocker use and improved survival.[272] Second, heterogeneity in neural innervation patterns—and their dynamic evolution during tumor development—also contributes to therapeutic variability. The PNS promotes proliferation, invasion, and metastasis through local neurotransmitter release, yet the density of nerve fibers and synaptic plasticity varies across tumor types and developmental stages.[26] Pancreatic cancer has dense local neural networks and exhibits "neural addiction", enhancing neural signaling through NGF-mediated axonogenesis.[273] In contrast, breast cancer relies heavily on non-neuronal mechanisms, particularly neurotransmitter receptor-mediated modulation of immune responses.[274] Additionally, neuroimmune crosstalk within the TME is highly tissue-specific. The SNS influences tumor cells, the microenvironment, and systemic physiology through adrenergic signaling, but immune cell responses to neurotransmitters differ across tumor types.[275] 5-HT, for example, enhances NK cells cytotoxicity and promotes T-cell activation.[276,277] In CRC, 5-HT promotes tumor progression by downregulating MMP12 in macrophages, thereby increasing angiogenesis in murine models of colon cancer.[278]

Although therapeutic strategies targeting neuro–tumor interactions have shown promising potential in cancer treatment—with capabilities such as immune activation and anti-metastatic effects—and multiple clinical studies have preliminarily validated their feasibility, particularly highlighting the value of neuromodulatory agents such as propranolol as adjunct therapies, caution is still warranted in clinical applications due to the complex and dynamic nature of nervous system–tumor interactions. Treatment approaches should be individualized based on cancer type, disease stage, and the specific neural components involved, and strengthened safety assessments and dynamic monitoring of neurotoxicity risks are crucial. Additionally, current research still exhibits considerable heterogeneity in treatment efficacy, underscoring the urgent need for larger-scale, prospective, multicenter clinical trials to further clarify the indications, target populations, and optimal strategies for combining these approaches with standard cancer therapies.

Clinical translation challenges and optimization pathways for neuro-targeted therapies

Therapeutic strategies targeting neuro–tumor interactions offer a novel approach to cancer treatment and have shown promising outcomes in various preclinical models and selected clinical studies.[34,72,73,231,235] However, multiple challenges remain in widespread clinical application, necessitating the coordinated advancement of mechanistic research and treatment standardization.

Limited identification of appropriate patient populations and tumor heterogeneity

Currently, clear stratification criteria for patients remain lacking, and the degree of neural regulation dependency varies substantially across tumor types and subtypes.[279–281] For

Table 4: Ongoing clinical trials involving neuron–cancer interactions.

Treatment	Diseases	Other treatment	Phase	Enrollment (*n*)	Trial number	Primary completion
Fluoxetine	Colorectal adenocarcinoma	No	Phase 2	10	NCT06225011	2025-12-01
Fluoxetine	Primary brain tumor	Temozolomide	Phase 2	30	NCT05634707	2025-12
Propranolol	Pancreatic cancer	Placebo	Phase 2	30	NCT06145074	2026-12-31
Propranolol	Colorectal neoplasms	Etodolac	Phase 2	200	NCT03919461	2027-02-28
Propranolol hydrochloride	Non-small cell lung cancer	Sintilimab, chemotherapy	Phase 1	6	NCT05979818	2025-08-31
Propranolol	Pancreatic neoplasms	Etodolac	Phase 2	210	NCT03838029	2026-01
Propranolol	Kaposi sarcoma	No	Phase 2	25	NCT05797662	2028-08-01
Propranolol	Advanced melanoma	Naltrexone	Phase 1	12	NCT05968690	2025-09-30
Propranolol hydrochloride	Kaposi sarcoma	No	Phase 2	25	NCT06445166	2027-03-31
Propranolol	Soft tissue sarcoma adult angiosarcoma and undifferentiated pleomorphic sarcoma	Pembrolizumab	Phase 2	80	NCT05961761	2028-01
Propranolol hydrochloride	Urothelial carcinoma	Pembrolizumab, nivolumab, avelumab	Phase 2	24	NCT04848519	2026-01-01
Propranolol hydrochloride	Esophageal adenocarcinoma (clinical stage II, III, IV), gastroesophageal junction adenocarcinoma (clinical stage III, IV)	Fluorouracil, leucovorin, oxaliplatin, pembrolizumab	Phase 2	40	NCT05651594	2026-03-30
Propranolol	Unresectable triple negative breast cancer	Pembrolizumab	Phase 2	25	NCT05741164	2026-12-15
Propranolol	Esophageal adenocarcinoma	Carboplatin, paclitaxel	Phase 2	106	NCT04682158	2027-04-01
Propranolol	Pancreatic cancer, hepatocellular cancer, biliary tract cancer, cholangiocarcinoma	Durvalumab, gemcitabine, tremelimumab, paclitaxel, cisplatin	Phase 2	62	NCT05451043	2025-10-01

example, the differential expression of β-AR in various tissues may influence responsiveness to β-blockers.[231,282] Yet many clinical studies have not stratified patients based on neural density, neurotransmitter signaling, or receptor expression, introducing potential bias.[283] Thus, it is critical to strengthen tumor subtyping based on neuro–tumor interaction characteristics—such as assessing intratumoral nerve density, neurotransmitter expression profiles, or innervation patterns—to build predictive models that aid in identifying suitable candidates for neuro-targeted interventions.

Complex therapeutic mechanisms and lack of standardized treatment regimens

Neuro-targeted therapies are often administered in combination with immune checkpoint inhibitors, chemotherapy, or surgery. However, overlapping mechanisms and unclear targets complicate treatment planning, and standardized protocols regarding timing and combinations are lacking.[3] Although a study has shown clinical benefits of propranolol and similar agents in certain cancers,[231] others have failed to demonstrate significant survival improvement in ovarian or prostate cancer (see the previous section). Therefore, well-designed, mechanism-based, and stratified randomized controlled trials are needed. These should integrate dynamic immune biomarkers and translational research to clarify specific mechanisms of action in different patient populations.

Potential nonspecific side effects and safety concerns

Although β-blockers are widely used in cardiovascular disease, long-term administration in patients with cancer may lead to adverse effects such as bradycardia, hypotension, fatigue, and cognitive dysfunction, particularly in older individuals or those with preexisting cardiovascular conditions. In addition, surgical neuro-interventions (such as vagotomy) are irreversible and may pose risks such as gastrointestinal dysfunction and postoperative infections.[73,284] Therefore, individualized dosing and treatment timing strategies should be developed, with preference for short-term perioperative interventions or dose reduction through combination therapy.[285]

Given the deleterious roles of neuropsychological factors in a variety of diseases, including cancer,[286] it is imperative to advance the clinical translation of neuro-targeted therapeutic strategies. This requires coordinated efforts across multiple dimensions, including mechanistic research, patient stratification, intervention design, and the standardization of clinical pathways. First, tumor subtyping based on neurobiological features should be reinforced. Tools such as nerve density scoring, neurotransmitter profiling, and receptor localization can support the development of predictive models for more precise patient selection and personalized therapy. Second, innovations in delivery strategies—such as local slow-release systems or targeted nanocarriers—are needed to enhance specificity and reduce systemic side effects. Simultaneously, the underlying biology of neuro-targeted therapy in diverse immune contexts remains to be fully elucidated. Mechanistically guided and stratified randomized trials, coupled with dynamic immune monitoring and translational studies, are essential for optimizing therapeutic combinations with standard treatments such as immunotherapy, chemotherapy, or radiotherapy. Ultimately, the successful clinical implementation of neuro–tumor interaction therapies depends on the establishment of a multidisciplinary, mechanism-informed, efficacy-predictable, and protocol-standardized treatment framework. Only then can neuro-targeted interventions become a valuable complement—and potentially a breakthrough direction—in cancer therapy.

Conclusion and Future Perspectives

The nervous system plays a critical and complex regulatory role in tumor initiation, progression, invasion, and metastasis. Increasing evidence indicates that tumors are not merely passive recipients of neural inputs; rather, they actively remodel neural structures and modulate neurotransmitter signaling pathways to construct a protumorigenic and immune-evasive "neuro–tumor niche". Elucidating this bidirectional interplay not only deepens our understanding of tumor biology but also opens new avenues for developing neuroregulation-based anticancer strategies. Therapeutic approaches targeting neural signaling pathways or neuron–tumor interactions may emerge as a promising frontier following advances in immunotherapy and metabolic therapy.

Future research should focus on several cutting-edge approaches. First, constructing an integrated multi-omics "neuro–tumor interactome" is essential for systematically delineating communication networks among neurons, immune cells, and tumor cells across different cancer types. Second, there is an urgent need to map the spatiotemporal dynamics of the neuro–immune microenvironment to identify critical regulatory nodes at distinct stages of tumor evolution. Third, innovative nanodelivery systems that recognize neuronal cues or respond to neural signals hold potential for precise therapeutic modulation at the neuro–tumor interface. Fourth, establishing cross-disciplinary collaborative platforms that integrate advances in neuroscience, immunology, and oncology is crucial for accelerating the clinical translation and individualization of neuro-targeted therapies. With ongoing research, strategies targeting the nervous system will offer breakthrough approaches in future anticancer treatment and provide new clinical techniques for improving patient outcomes and quality of life.

Funding

This work was supported by grants from the Sichuan Science and Technology Program (No. 2025ZNSFSC0559), the National Natural Science Foundation of China (No. 82573560), and 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (No. ZYGD23014).

Conflicts of interest

None.

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How to cite this article: Zhou L, Luo X, Bao TJ, Sun HB, He CQ, Yang YH, Xia Y. Neurobiology of cancer: Unraveling the roles of the nervous system in tumor initiation, progression, and therapeutic. Chin Med J 2026;XXX:1–28. doi: 10.1097/CM9.0000000000004144