Molecular Cancer

REVIEW

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Cancer-nervous system crosstalk: from biological mechanism to therapeutic opportunities

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Abstract

A growing body of research suggests a bidirectional interaction between cancer and the nervous system. Neural cells exert their effects on tumors by secreting neurotransmitters and cell adhesion molecules, which interact with specific receptors on tumor cells to modulate their behavior. Conversely, tumor-secreted factors, particularly including inflammatory factors, can alter neural activity and increase neuronal excitability, potentially contributing to neurological manifestations such as epilepsy. The immune system also serves as a crucial intermediary in the indirect communication between cancer and the nervous system. These insights have opened promising avenues for novel therapeutic strategies targeting both tumors and their associated neurological complications. In this review, we have synthesized the key biological mechanisms underlying cancer-nervous system interactions that have emerged over the past decade. We outline the molecular and cellular pathways mediating this cross-talk and explore the clinical implications of targeting the nervous system to suppress tumor growth and metastasis, mitigate neurological complications arising from cancer progression, and modulate the immune response through neural regulation in the context of cancer therapy.

Keywords Cancer, Neurobiology of cancer, Oncological therapeutic modalities, Nervous system

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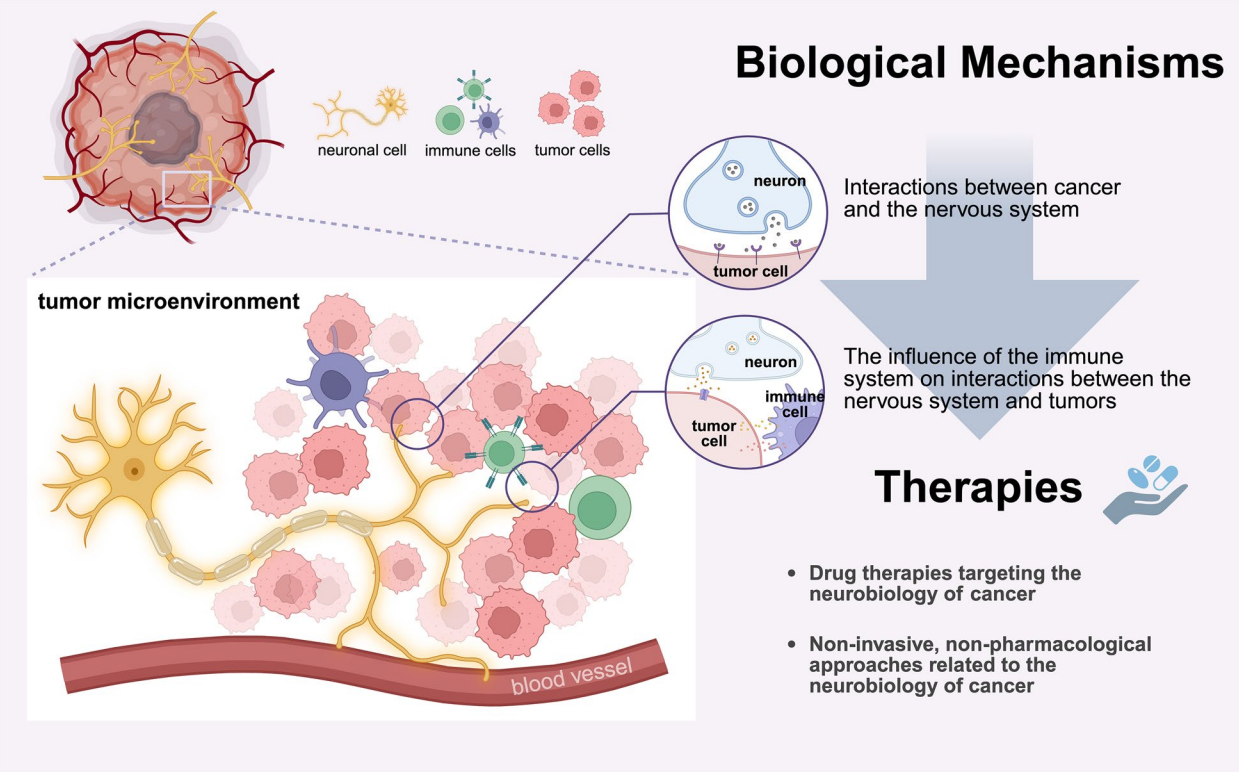
Graphical Abstract



Background

The recognition that the nervous system plays an active and complex role in tumor growth and progression represents a pivotal advancement in the field of oncology [1]. Early observations of the interaction between the nervous system and tumors date back to the latter half of the nineteenth century. During this period, autopsies of patients with advanced esophageal and tongue cancers revealed that tumor expansion could compress and damage adjacent nerves, resulting in neurological dysfunction [2, 3]. At that time, nervous tissue was largely regarded as a passive structure, much like muscle or connective tissue, that was secondarily affected by tumor invasion. Consequently, the potential active role of the nervous system in cancer progression remained largely underappreciated [4–7]. In the ensuing decades, researchers gradually identified phenomena such as perineural invasion (PNI) [8, 9] and demonstrated that tumor-derived factors could induce peripheral nerve inflammation even in regions not directly invaded by the tumor [10]. Concurrently, studies revealed that neurotrophic factors secreted by nerves, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), could facilitate tumor proliferation and survival [11]. However, despite these findings, the conceptual framework for understanding neurotumoral interactions remained relatively stagnant. The real turning point came in 2013, when Magnon et al. demonstrated for the first time in a mouse model of prostate cancer that nerve fibers can grow out of tumor tissue through the process of axonogenesis, thereby promoting cancer growth and spread [12]. Subsequent validation in mouse models of breast [13], gastric [14], and lung cancers [15] has confirmed the presence of infiltrating autonomic and sensory nerve fibers within tumor tissues, releasing neurotransmitters that engage with their specific receptors on both stromal and cancer cells [16, 17]. These discoveries have transformed our understanding of cancer-nerve interactions and have given rise to a new interdisciplinary field: cancer neurobiology.

The emerging field of cancer neurobiology has garnered increasing attention in recent years, as the pivotal role of the nervous system in cancer development and progression has become increasingly evident. Recent

research indicates that neural activity is crucial for the development of hallmark cancer capabilities [18]. Specifically, neuronal activity has been shown to modulate the immune response and facilitate cancer cells' ability to escape immune surveillance [19]. Moreover, accumulating evidence has uncovered multiple modes of communication between cancer cells and neurons, highlighting the complexity of their bidirectional interactions. Particular attention has also been directed toward the interplay between the nervous system and the tumor microenvironment, which plays a pivotal role in shaping tumor behavior and therapeutic response [18, 20]. This evolving understanding suggests that targeting neural-tumor interactions represent a promising therapeutic strategy. For instance, denervation approaches have been shown to slow or even halt tumor growth in preclinical models. Additionally, pharmacological inhibition of specific neurotransmitter receptors, such as M3 muscarinic and metabotropic glutamate receptor 1 (mGluR1), has demonstrated efficacy in suppressing tumor progression, thereby emerging as a viable oncological intervention [21]. Advancements in cancer neurobiology are thus essential for elucidating the intricate crosstalk between the nervous system and cancer. They provide novel insights into tumor biology and pave the way for innovative treatment strategies. The objective of this review is to elucidate the molecular mechanisms underlying neural-tumor interactions, outline the principal signaling pathways involved, and summarize recent breakthroughs in the field. Furthermore, the review evaluates the therapeutic potential of newly developed neural-targeted interventions and explores their implications for improving clinical outcomes in cancer patients.

Interactions between cancer and the nervous system

The role of neural activity in cancer progression

Neuronal activity promotes cancer growth

Neuronal activity contributes to tumor development and growth through various mechanisms, such as direct interaction with tumor cells, indirect modulation of the immune system and alterations in tumor vascularization. Current research predominantly focuses on the roles of neurotransmitters and neurotrophic factors secreted by neurons, which bind to specific receptors on tumor cells and directly influence their growth and survival. Neurotransmitters in the synaptic cleft, such as adrenaline, norepinephrine, dopamine, acetylcholine, glutamate, etc., along with neurotrophic factors, such as BDNF, NGF, Neurotrophin-3, etc., and neurogenic chemokines, such as C-X-C motif chemokine ligand 12 (CXCL12) and C-X3-C motif chemokine ligand 1 (CX3CL1), etc., can interact with corresponding receptors on tumor cells (Fig. 1A). These interactions activate a range of downstream signaling cascades that support tumor growth, invasion, and metastasis [22, 23]. Tumor cells frequently exhibit dysregulated expression and function of ion channels and neurotransmitter receptors, rendering them more susceptible to modulation by neuronal signals. This dysregulation contributes to unchecked proliferation and dissemination [24, 25]. For example, the excitatory neurotransmitter glutamate activates the N-methyl-D-aspartate receptor (NMDAR) on tumor cells, triggering downstream pathways such as Calcium/Calmodulin-Dependent Protein Kinase II/IV (CaMKII/IV) and mitogen-activated extracellular signal-regulated kinase (MEK)-mitogen-activated protein kinase (MAPK). These pathways ultimately lead to the activation of the transcription factor cAMP response element-binding protein (CREB), promoting tumor growth and invasiveness [26] (Fig. 1B). Similarly, neurotrophic factors, including BDNF, NGF and Neurotrophin-3, activate neurotrophic factor receptors like p75 neurotrophin receptor (p75 NTR), tropomyosin receptor kinase B (TrkB), and tropomyosin receptor kinase C (TrkC) on tumor-initiating cells, enhancing their vitality through the extracellular signal-regulated kinase (ERK) and Ak strain transforming (AKT) pathways [27, 28] (Fig. 1B).

Building on the direct effects of neuronal activity on tumor cells, it is also important to explore the indirect

(See figure on next page.)

Fig. 1 Different pathways of neural influence on tumors: **A**. Neurons act on tumor cells via neurotransmitters, neurotrophic factors, neurogenic chemokines, etc., through corresponding receptors. **B**. By secreting glutamate, neurons bind to glutamate receptors, such as NMDAR, AMPAR, etc., on tumors to promote tumor growth and invasion. Neurons can also promote tumor growth and invasion by secreting neurotrophic factors that bind to tumor receptors. **C**. Neurons secrete neurotransmitters such as acetylcholine and GABA to act on tumor cells, triggering tumor immune escape. **D.** Neurons secrete MDK to activate $CD8^+$ T cells and promote the secretion of CCL4, enhancing CCL5 expression in microglial cells, thereby mediating cancer cell proliferation. **E**. Neurons promote angiogenesis in the tumor microenvironment by secreting norepinephrine (NE), providing nutrients for tumor growth. **F**. Tumor cells form a network through TM and TNT, where neurons may regulate TM and TNT formation. **G-I**. The interaction mechanism between the nervous system and tumors. **G**. Schwann cells envelop cancer cells, forming synchronized tissue patterns of Schwann cells and cancer cells, termed TAST. **H**. Activated Schwann cells secrete CCL2, recruiting monocytes that differentiate into macrophages and secrete cathepsin B, promoting PNI of tumors. **I**. Schwann cells secrete IL-6 and CXCL5, acting on tumor cells to activate STAT3 and Phosphatidylinositol 3-kinase (PI3K)/AKT/GSK-3β pathways, enhancing cell migration

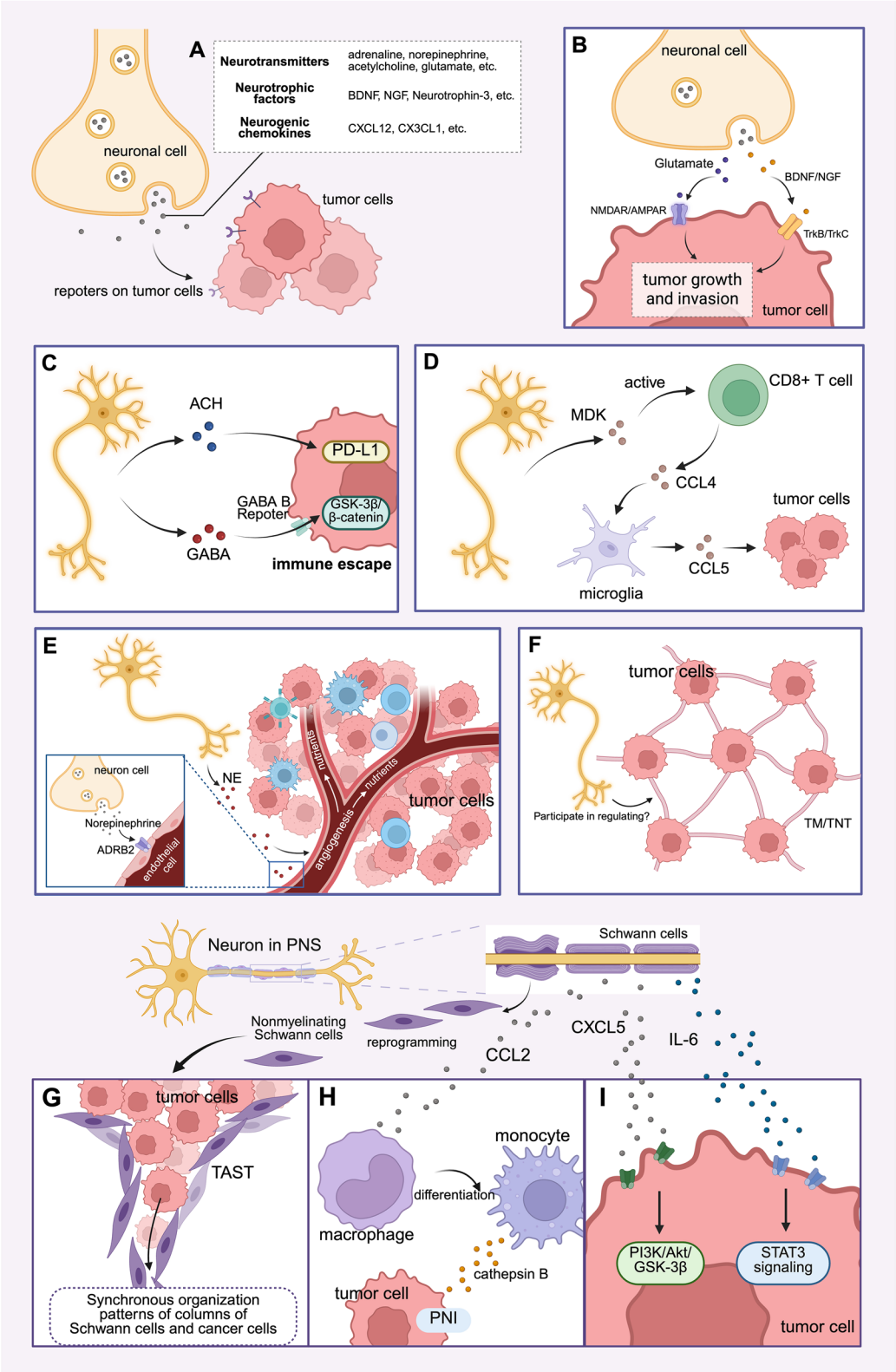


Fig. 1 (See legend on previous page.)

roles neurons play in modulating the tumor microenvironment, particularly in facilitating immune evasion. During tumor growth, cancer cells acquire the ability to evade immune surveillance, thereby avoiding recognition and elimination by the host immune system. Neurons contribute to this process not only by acting directly on tumor cells to induce immune escape mechanisms but also by modulating the function of immune cells within the tumor microenvironment. This neuronal influence diminishes the immune system's capacity to effectively detect and eliminate malignant cells. For example, the neurotransmitter acetylcholine has been shown to upregulate the expression of the immune checkpoint molecule Programmed cell death 1 ligand 1 (PD-L1) on tumor cells, thereby conferring resistance to cytotoxic $CD8^+$ T cells [29] (Fig. 1C). Similarly, the inhibitory neurotransmitter γ-Aminobutyric Acid (GABA) activates $GABA_B$ receptors on cancer cells, suppressing Glycogen Synthase Kinase 3β (GSK-3β) activity, thereby enhancing β-catenin signaling. This cascade not only promotes tumor cell proliferation but also impedes $CD8^+$ T cell infiltration into the tumor microenvironment [30] (Fig. 1C). Moreover, neurons can produce Midkine (MDK), a neurotrophic factor that modulates T cell activity. MDK stimulation leads to increased expression of the pro-inflammatory chemokine C-C motif chemokine ligand 4 (CCL4) by $CD8^+$ T cells. This activation of $CD8^+$ T cells and subsequent production of CCL4 result in insufficient T cells in the tumor microenvironment to recognize and eliminate tumor cells. Additionally, the production of CCL4 can promote the nuclear factor κB (NF-κB)-dependent expression of C-C motif chemokine ligand 5 (CCL5) by microglial cells, which in turn activates the AKT/GSK-3β/CREB pathway, promoting tumor cell proliferation and resistance to apoptosis [18, 31] (Fig. 1D). In addition to immune modulation, neuronal activity also supports tumor growth by promoting angiogenesis, ensuring a continuous nutrient supply. Sympathetic nerve-derived norepinephrine activates adrenoceptor β2 (ADRB2) on endothelial cells, reprogramming their metabolism toward aerobic glycolysis to facilitate angiogenesis within the tumor microenvironment [32, 33] (Fig. 1E).

In summary, neuronal activity regulates both direct and indirect regulatory effects on tumor biology, influencing cancer progression through multiple interrelated mechanisms. Although cancer neurobiology is still in its infancy, growing evidence has unveiled diverse neural pathways that contribute to tumor development. These insights offer promising avenues for therapeutic intervention. Future research should focus on elucidating the specific roles of various neuronal and glial subtypes in tumor-nervous system interactions. Moreover, understanding the differential contributions of the central versus peripheral nervous systems to cancer progression represents a critical direction for further investigation.

Neuronal activity promotes cancer metastasis

In addition to its role in tumor initiation and proliferation, neuronal activity significantly contributes to cancer metastasis by enhancing tumor cell invasiveness. Neurons secrete a variety of neurotransmitters and neurotrophic factors that modulate gene expression and facilitate direct communication between tumor cells, thereby increasing malignancy and metastatic potential. For example, norepinephrine can upregulate human telomerase reverse transcriptase (hTERT) expression via the ADRB2/p21-activated kinases (PAK)/Src/hypoxia-inducible factor 1α (HIF-1α) and cellular MYC (c-MYC) signaling pathways, promoting epithelial-mesenchymal transition (EMT) and facilitates the invasion of ovarian cancer cells.

Beyond molecular signaling, tumor cells can form specialized membrane-bound tubular structures: such as tumor microtubes (TMs) and tunneling nanotubes (TNTs), which allow long-distance intercellular communication and contribute to cancer invasion, therapy resistance, and metastasis [33, 34] (Fig. 1F). Under stress conditions, tumor cells generate these structures to transfer cellular components, including organelles, RNA, proteins, and signaling molecules, to neighboring or damaged cells, thereby enhancing the resilience and survival of recipient cells [35]. In gliomas, the formation of TMs has been linked to neuron-associated proteins such as growth-associated protein 43 (GAP-43) and tweety-homolog 1 (Ttyh1), which also facilitate microtubule-dependent tumor cell proliferation, invasion, interconnectivity, and radioresistance [36]. Although a direct regulatory role of neurons in TM or TNT formation has yet to be confirmed, the involvement of neuron-associated proteins suggests potential crosstalk between neural signaling and these metastatic pathways. Targeting TM and TNT formation mechanisms, especially those involving neural components, could complement traditional cancer therapies by reducing metastatic spread and recurrence.

Non-neuronal cells of the nervous system, particularly glial cells, also play essential roles in supporting tumor metastasis. Schwann cells, a key component of the peripheral nervous system, undergo morphological and metabolic reprogramming that facilitates tumor migration and invasion [37, 38]. Within the pancreatic cancer microenvironment, Schwann cells are reprogrammed via c-Jun-dependent pathways typically associated with nerve injury, transitioning to a non-myelinating

phenotype. These reprogrammed Schwann cells enwrap pancreatic cancer cells, forming organized cellular columns that guide tumor cells into aligned chains, thereby establishing migratory routes known as tumor-activated Schwann cell trajectories (TAST) [37] (Fig. 1G). In addition to providing structural guidance, these demyelinated Schwann cells can exert mechanical tension to further accelerate tumor dissemination. Activated Schwann cells secrete the chemokine C-C motif chemokine ligand 2 (CCL2), which recruits inflammatory monocytes that differentiate into macrophages capable of expressing the extracellular protease cathepsin B. These macrophages, along with cathepsin B, contribute functionally to PNI, along with cathepsin B, contribute functionally (Fig. 1H). Moreover, co-culture studies have demonstrated that Schwann cell-derived interleukin-6 (IL-6) promotes pancreatic cancer cell migration and invasiveness via activation of the Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathway. This effect is abrogated by IL-6 neutralization or STAT3 downregulation, confirming the functional role of this axis in tumor progression [39] (Fig. 1I). Similarly, Schwann cells can secrete CXCL5, which interacts with CXCR2 receptors on lung cancer cells. This interaction activates the PI3K/AKT/GSK-3β pathway, upregulating EMT regulators such as Snail and Twist and thereby enhancing cancer cell motility and metastatic potential [40].

Collectively, these findings underscore the multifaceted role of the nervous system in facilitating cancer metastasis. Both neuronal and glial components actively participate in shaping a pro-metastatic microenvironment through molecular signaling, structural remodeling, and immune modulation. Elucidating the precise mechanisms of neural regulation in cancer dissemination may pave the way for novel therapeutic strategies aimed at disrupting these neural-tumor interactions. More detailed information about neuronal activity in cancer progression and metastasis is provided in the table (Table 1).

Cancer impact on neural function

Cancer-released neurotrophins induce nerve outgrowth

Tumors can significantly influence the nervous system by releasing neurotrophins and axon guidance molecules that promote nerve growth and axonogenesis [11, 20]. These factors contribute to the sprouting of new nerve fibers within malignant tissues, effectively linking the tumor microenvironment to the nervous system [17]. NGF, a classical neurotrophin essential for neuronal growth and development, is aberrantly expressed in various types of tumor cells and serves as a biomarker of tumor progression [60]. In a mouse model of pancreatic ductal adenocarcinoma (PDAC), elevated expression and secretion of both NGF and BDNF have been observed [61]. Similarly, increased NGF levels have been reported in colorectal, breast and pancreatic cancers [62, 63], and these tumors exhibit a markedly higher density of newly formed sympathetic nerve fibers compared to their normal tissue counterparts [64]. As tumors expand, these newly formed nerves can extend toward and integrate with the central nervous system. BDNF, another critical neurotrophic factor, regulates synaptic plasticity and promotes the growth, differentiation, and maturation of both central and peripheral neurons [65, 66]. High expression of BDNF in tumor tissues has been correlated with increased tumor invasiveness and a higher propensity for brain metastasis [67]. In pancreatic cancer, tumor-derived BDNF activates Trk receptors, stimulating neuronal axonogenesis and altering neural composition within the brain. Collectively, these findings underscore the role of neurotrophins such as NGF and BDNF as molecular bridges between tumors and the nervous system, facilitating aberrant neural remodeling (Fig. 2A).

In addition to neurotrophins, axon guidance molecules play a pivotal role in tumor-nerve crosstalk. These molecules, initially characterized for their role in directing neuronal axon outgrowth, are now known to be closely associated with tumor development and progression [68]. Key axon guidance families include Plexins/Semaphorins, Erythropoietin-producing hepatocellular carcinoma (Eph)/Eph-family receptor-interacting proteins (Ephrin), Netrins and their receptors, Slit-Robo, all of which are expressed in various malignancies and contribute to cancer cell invasion, migration, and metastasis [69, 70]. For example, in prostate cancer, tumor cells were found to express high levels of semaphorin 4F (S4F), an axon guidance molecule that induces neurite sprouting and elongation when co-cultured with neurons, indicating its role in promoting neural innervation of tumors [71] (Fig. 2B). Another prominent axon guidance system, the Eph/Ephrin axis, comprises Eph receptor tyrosine kinases and their membrane-bound ephrin ligands. This system is highly expressed in tumor tissues and is linked to angiogenesis, invasion, metastasis, and the maintenance of cancer stem cell populations. Recent studies have demonstrated that tumor-derived exosomes enriched with ephrin-B1 can stimulate neurite outgrowth in PC12 cells, suggesting that Eph/Ephrin signaling also contributes to tumor innervation [72] (Fig. 2B). Similarly, netrin-1, a molecule implicated in axonal pathfinding, is highly expressed in many aggressive cancers and binds to the deleted in colorectal cancer (DCC) receptors to activate axon regeneration pathways [73]. In the peripheral nervous system, Schwann cells can utilize netrin-1 as a guidance cue via DCC receptors expressed on regenerating axons, facilitating neural repair and potentially supporting PNI in cancer [74] (Fig. 2C).

Table 1 Neuronal activity in cancer progression and metastasis

System	Cancer Type	Subtype/Classification	Neuronal Activity Mechanism	Related Molecules/Pathways
Digestive System	Gastric Cancer	Adenocarcinoma	CGRP peptidergic neurons directly connect to gastric cancer spheroids. Chemogenetic activation of these neurons induces calcium release into the cytoplasm of cancer cells, thereby promoting tumor growth and metastasis [41]	CGRP, Ca^{2+}
	Colorectal Cancer	-	Overexpression of NGF during colorectal carcinogenesis activates the TrkA-MAPK/ERK pathway, upregulates NGAL expression, enhances MMP2 and MMP9 activity, and promotes colorectal cancer metastasis [42]	NGF, TrkA-MAPK/ERK, NGAL, MMP2, MMP9
	Liver Cancer	Intrahepatic cholangiocarcinoma (ICC)	Parasympathetic-derived acetylcholine induces epithelial-mesenchymal transition (EMT), thereby promoting ICC metastasis [43]	CAMKII, GSK3β/β-catenin, BDNF
	Pancreatic Cancer	Ductal Adenocarcinoma (PDAC)	Neurogenic chemokines CXCL12 and CX3CL1 facilitate tumor cell invasion of nerves via their respective receptors CXCR4 and CX3CR1 [44, 45]	CXCL12, CX3CL1, CXCR4, CX3CR1
			The chemokine CCL7, produced by Schwann cells, enhances PDAC cell migration, invasion, and tissue inhibitor of matrix metalloproteinases 1 (TIMP1) expression via the CCR1/STAT2 pathway. TIMP1 further stimulates Schwann cell proliferation and migration through CD63/PI3K/AKT signaling [46]	CCL7, CCR1/STAT2, CD63/PI3K/AKT
			Catecholamines, such as NE, released from sympathetic nerves act on ADRB2 in PDAC cells, promoting the invasion and metastasis of cancer through the activation of the ADRB2/PKA/STAT3 signaling pathway. This process also increases the production of NGF and MMP2/9 [47]	NE, ADRB2/PKA/STAT3, NGF, MMP2/9
Respiratory System	Lung Cancer	Small Cell Lung Cancer (SCLC)	Neuronal activity supports SCLC cell survival by activating the $G\alpha_s$/cAMP/PKA/CREB signaling axis; disruption of this pathway promotes tumor cell death via JNK/c-Jun activation [48]	$G\alpha_s$/cAMP/PKA/CREB, JNK/c-Jun
			Targeting the neuronally expressed Notch ligand DLL3 in SCLC does not improve survival, suggesting that tumor-associated neuronal markers may not always be effective therapeutic targets [49, 50]	DLL3, KEAP1/NRF2/Notch
		Non-Small Cell Lung Cancer (Adenocarcinoma)	Neuronatin (NNAT) promotes NSCLC progression by enhancing tumor innervation via NGF [51]	NF-κB pathway
			Lung cancer cells may promote immune evasion by inducing NK cell apoptosis through the neuronal-like p75 NTR-proNGF-sortilin signaling axis [52, 53]	proNGF/p75 NTR

Table 1 (continued)

System	Cancer Type	Subtype/Classification	Neuronal Activity Mechanism	Related Molecules/Pathways
Urinary System	Prostate Cancer	Neuroendocrine Type	The upregulated NGF promotes NEPC development by integrating CHRM4 and activating the AKT-MYCN pathway [54]	NGF-CHRM4 axis
		-	In the prostate cancer microenvironment, the loss of P-adrenergic signaling exerts a significant inhibitory effect on both tumor growth and angiogenesis [32]	Adrenergic nerves, ADRB2 signaling, Coa6
			Autonomic Nerve Development effects the Progression of Prostate Cancer [12]	Adrenergic signals, ADRB2 and ADRB3, Cholinergic signals, CHRM1
	Renal Cancer	-	Neuron-derived neurotrophic factor suppresses RCC progression by inhibiting EMT, reducing cell proliferation, and promoting G1 to S phase cell cycle arrest [55]	Cyclin D1, Vimentin, MMP-7, Wnt/β-catenin signaling, Ras signaling
Endocrine System	Breast Cancer	Triple-Negative Breast Cancer (TNBC)	Neurons bind to β2-AR on TNBC by secreting NE, promoting the progression of cancer [56]	NE/β2-AR signaling
			Neuronal proNGF promotes brain metastasis of triple-negative breast cancer cells through the TrkA/EphA2 pathway [57]	TrkA/EphA2
		-	Parathympathetic nerve secretes BDNF and NGF, acts on TrkA and TrkB receptors on breast cancer cells, activates downstream Akt/PI3K, Jak/STAT, NF-kB, Wnt/β-catenin pathways, and promotes cancer migration, proliferation, and angiogenesis [58]	Akt/PI3K, Jak/STAT, NF-kB, Wnt/β-catenin pathways
			GABA secreted by neurons binds to GABAR on breast cancer, activates downstream ERK1/2 pathway, and promotes cancer metastasis [59]	ERK1/2 pathway

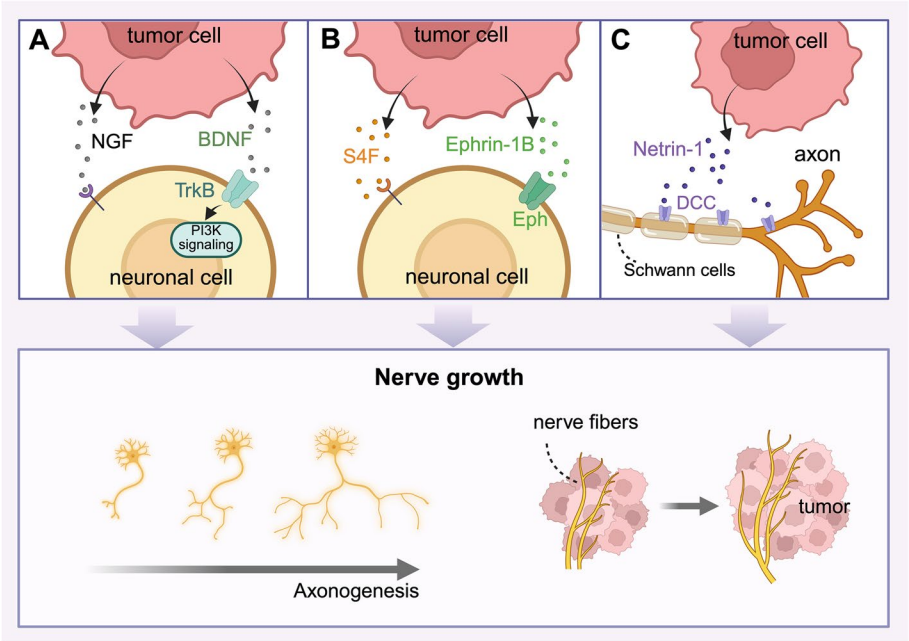


Fig. 2 The mechanisms of cancer cell impact on neural function: **A**. Tumor cells release neurotrophic factors (such as NGF and BDNF) that bind to receptors on neurons, promoting axonogenesis and nerve growth. **B**. Tumor cells secrete axon growth factors, such as S4F and Ephrin-B1, which bind to corresponding receptors on neurons, facilitating axonogenesis. **C**. Tumor-derived Netrin-1 binds to DCC receptors expressed on neuronal axons and Schwann cells, guiding axonal regeneration across peripheral nerve bridges

Beyond secreted factors, tumors may promote nerve development through alternative mechanisms. In small cell lung cancer, axonogenesis-related genes and neural migration pathways are upregulated in malignant epithelial cells. These cancer cells exhibit morphological changes reminiscent of neuronal cells and form nerve-like intercellular connections. Furthermore, a subset of cancer stem cells (CSCs) isolated from gastric and colorectal cancer patients has been shown to differentiate into neuron-like cells in vitro, including both sympathetic and parasympathetic subtypes, indicating that tumors may actively participate in neurogenesis [75]. Therefore, future research into cancer-neuron interactions may entail examining the morphological and functional analogies between cancer cells and neurons, along with the identification of their principal pathways.

Cancer-derived neuropeptides cause neuropathic pain

Pain is one of the most prevalent and debilitating symptoms experienced by cancer patients, substantially compromising their quality of life. A substantial body of research now substantiates the inextricable link between cancer-induced pain and the infiltration of macrophages [76–78]. Among the mediators of this pain, cancer-derived neuropeptides such as calcitonin gene-related peptide (CGRP) and neuropeptide Y (NPY), have been shown to hyperactivate injured peripheral nerve endings, thereby triggering neuropathic pain [79–81]. Moreover, tumors generate excessive glycolytic metabolites, creating a highly acidic tumor microenvironment. This acidification influences the function of cation channels on peripheral sensory neurons, leading to their sensitization and the development of cancer-induced bone pain [82]. In the following sections, we elaborate on the molecular mechanisms underlying tumor-nerve crosstalk and its role in cancer-associated pain.

Neurotrophic factor plays a pivotal role in the pathogenesis of cancer pain. In pancreatic cancer, both malignant and infiltrating immune cells release NGF, which binds to TrkA on sensory neurons, promoting neuronal activation and recruitment [83] (Fig. 3A). This process facilitates perineural infiltration, thereby inducing pain. In the Methyl-N-nitrosourea-induced Rat Mammary Tumor-1 (MRMT-1) model of bone cancer, NPY expression is significantly upregulated, further supporting the involvement of neuropeptides in tumor-induced pain [84]. Furthermore, NGF, along with other neurotrophic factors, can activate the transient receptor potential vanilloid type 1 (TRPV1) receptor [85] (Fig. 3B). As a member of the thermosensitive TRP channel family, TRPV1 responds to thermal, mechanical, and chemical stimuli. Its activation leads to sensory neuron depolarization and the subsequent release of CGRP and substance P (SP), which

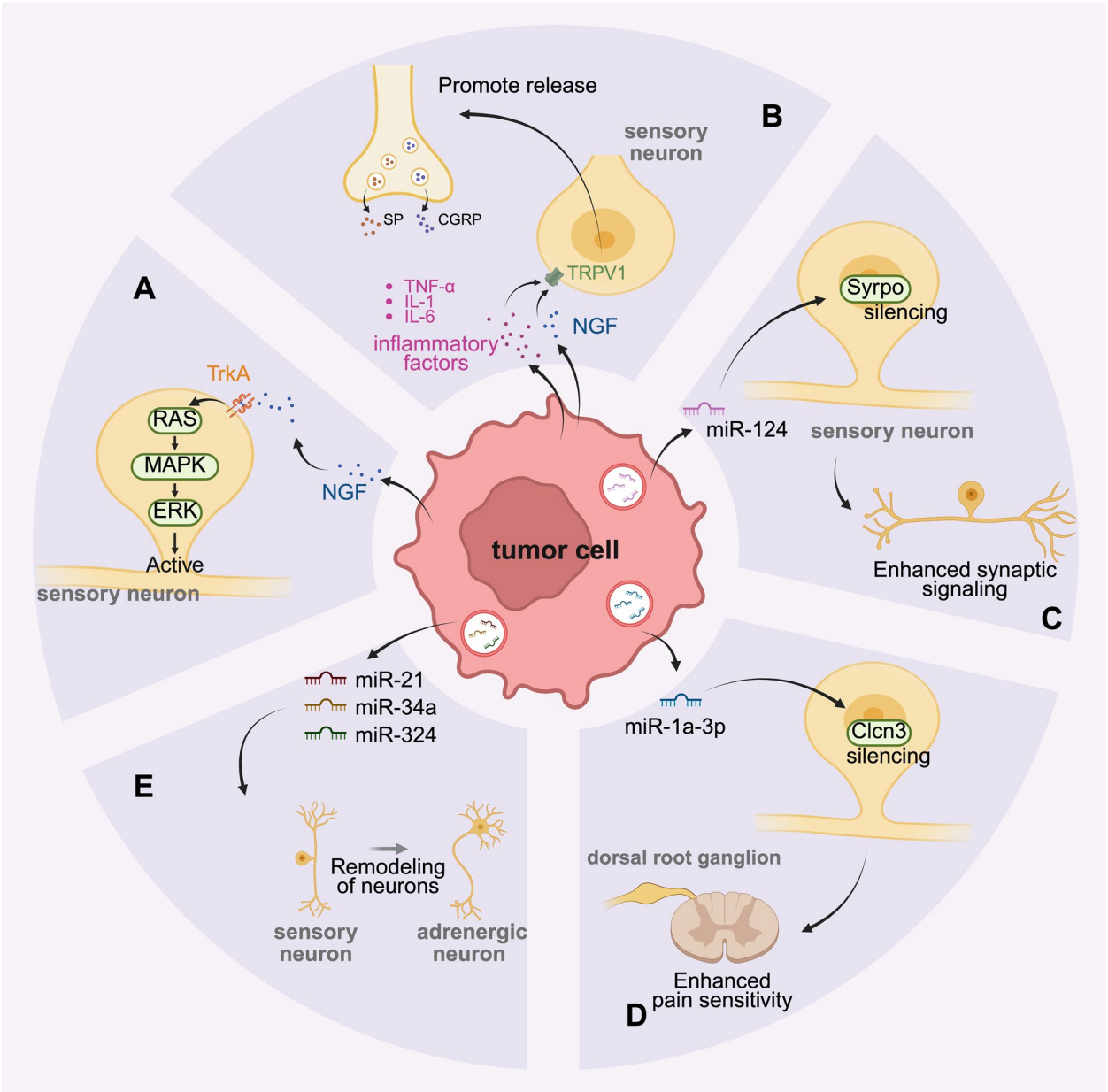


Fig. 3 Mechanisms by which tumor cells promote cancer pain: **A**. Tumor cells release NGF, which acts on TrkA receptors on sensory neurons, activating them through the RAS/MAPK/ERK pathway and transmitting pain signals. **B**. Tumor cells release inflammatory cytokines (e.g., TNF-α, IL-1, IL-6) and neurotrophic factors (e.g., NGF), targeting TRPV1 receptors on sensory neurons and promoting the secretion of pain-inducing substances such as SP and CGRP by these neurons. **C-E**. Tumor cells also influence sensory neurons through the secretion of miRNAs. **C**. Tumor cells release less miR-124, which allows for increased expression of the *Synpo* gene, promoting synaptic signal transmission and enhancing pain sensitivity. **D**. Tumor cells release miR-1a-3p, which acts on neurons to silence the *Clcn3* gene, increasing the sensitivity of dorsal root ganglia. **E**. Tumor cells secrete miR-21, miR-34a, and miR-324, leading to the reprogramming of sensory neurons into adrenergic neurons. The activation of endogenous pain-related genes in these neurons can intensify the pain experienced by cancer patients

facilitate pain transmission [86, 87]. For instance, models of bone cancer pain, TRPV1 is activated not only by metabolic byproducts such as formaldehyde but also by inflammatory mediators including tumor necrosis factor α (TNF-α), Interleukin-1 (IL-1), and IL-6, all of which are secreted by cancer cells [88, 89] (Fig. 3B). This activation enhances the sensitivity of dorsal root ganglia (DRG) neurons, contributing to the perception of pain [90]. Notably, in a melanoma model, either TRPV1 knockdown or CGRP receptor

inhibition significantly impaired tumor growth and increased survival in mice bearing B16F10 melanoma cells. Furthermore, TRPV1 expression across various immune cell types suggests a potential role in anti-tumor immune responses, a topic warranting further investigation [91, 92].

MicroRNAs (miRNAs) have emerged as critical regulators of neuropathic pain, influencing neuronal development, plasticity, and function [93–96]. In cancer, miRNAs packaged into tumor-derived extracellular vehicles (EVs) are differentially expressed and can modulate both the tumor microenvironment and neural signaling pathways (Fig. 3C-E). In a bone cancer pain model, a marked downregulation of miR-124 was detected in the spinal cord, correlating with enhanced pain signal transmission from the spinal cord to the brain [97] (Fig. 3C). This effect is partly mediated by miR-124's suppression of Synaptopodin (Synpo), a key protein in synaptic transmission. Meanwhile, miR-1a-3p was shown to exacerbate pain sensitivity in sensory neurons of the DRG by targeting the *Clcn3* chloride channel gene [98] (Fig. 3D), highlighting the functional impact of specific miRNAs in pain regulation. This underscores the potential of miRNAs as therapeutic targets and biomarkers in cancer pain management. The aforementioned experimental findings indicate that miRNAs may serve as intermediaries in tumor-nerve interactions, modulating the transmission of cancer pain signals. Amit et al. reported significant findings in a p53-deficient oral squamous cell carcinoma (OCSCC) mouse model, where the expression of extracellular vesicles harboring specific miRNAs, namely miR-21, miR-34a, and miR-324, was diminished [99] (Fig. 3E). This reduction in miRNA-enriched extracellular vesicles from cancer cells was observed to trigger a restructuring of the existing sensory neurons, facilitating their transformation into adrenergic nerves. The activation of endogenous pain-related genes within these sensory neurons, such as *Ntrk2*, *Tac1*, and *Plcg1*, was identified as a mechanism that intensifies the experience of cancer pain [99].

In summary, cancer-associated pain results from a complex interplay of tumor-derived signals, immune responses, and neuronal adaptations. While inflammation plays a contributory role, a significant portion of cancer pain is neuropathic in origin, driven directly by cancer cells through the release of neuropeptides, the activation of cation channels such as TRPV1, and the modulation of neural gene expression by miRNAs. Together, these molecular and cellular events constitute a multifaceted mechanism through which tumors induce and sustain pain. Understanding these pathways not only offers insights into the biology of cancer pain but also provides promising targets for its effective management.

Cancer-nervous system related pathways

The interaction between the nervous system and tumors is multifaceted and dynamic, contributing significantly to cancer progression. With growing insight into the cancer-promoting effects of neural activity, an increasing number of signaling pathways linking the nervous system to tumor development have been identified and experimentally validated. These pathways play critical roles in modulating tumor cell behavior, including proliferation, invasion, and metastasis. In this section, we summarize key nervous system-related pathways that have been elucidated in recent years (Table 2).

Cholinergic receptor-related pathways

Cholinergic receptors, membrane-bound proteins that bind acetylcholine, are widely expressed throughout the central and peripheral nervous systems. Based on their pharmacological and molecular properties, they are broadly categorized into two major groups: nicotinic cholinergic receptors (nAChRs) and muscarinic cholinergic receptors (mAChRs). A growing body of evidence suggests that these receptors play critical roles in mediating nervous system-driven tumorigenesis and metastasis (Fig. 4A).

mAChRs are classified into five subtypes, M1 to M5, encoded by the genes cholinergic receptor muscarinic 1 (CHRM1) to cholinergic receptor muscarinic 5 (CHRM5). Each subtype contributes uniquely to neural-tumor signaling loop. Recent studies have confirmed that in PDAC mice, muscarinic agonists can rescue cancer progression in vagotomized mice. Specifically, activation of CHRM1 inhibits the epidermal growth factor receptor (EGFR)/MAPK/PI3K/AKT signaling cascade. Enhanced cholinergic signaling also suppresses cancer stem cell (CSC) populations, $CD11b^+$ myeloid infiltration, TNF-α production, and hepatic metastatic growth, ultimately prolonging survival in PDAC-bearing mice [100]. In gastric cancer, Yu et al. demonstrated that tumor cells are capable of synthesizing and secreting acetylcholine, leading to autocrine and paracrine activation of muscarinic acetylcholine receptor 3 (M3R), which induces gastric cancer cell proliferation through trans-activation of EGFR signaling [101]. Furthermore, cholinergic signaling in $Dclk1^+$ cell clusters within the gastric epithelium have been shown to induce NGF expression, which in turn stimulates cholinergic neuron growth, forming a positive feedback loop that sustains tumor-nerve interactions [102]. Similar tumor-promoting effects of M3R have been observed in pancreatic and colorectal cancers

Table 2 Cancer-nervous system related pathways

Neurosecretory factors	Receptors on tumor cells	Related pathways	Tumor changes
Acetylcholine	CHRM1	EGFR/MAPK/PI3K/AKT [100]	Inhibits cancer progression, reduces inflammation
	CHRM1 (in stroma) [54]	Unspecified	Promotes prostate tumor growth and metastasis
	CHRM3	EGFR transactivation [101]	Promotes gastric cancer proliferation
		NGF induction, cholinergic neuron growth [102]	Establishes tumor-nerve feedback loop
	CHRM4	AKT [54]	Induces neuroendocrine differentiation and invasion
	CHRNA5	Ca^{2+}/CaMKII/GSK-3β/β-catenin [43]	Enhances β-catenin, BDNF expression, metastasis, drug resistance
Catecholamines	ADRB2	ETV1/c-KIT/MAPK [106–108]	Promotes tumorigenesis in GIST
		AKT/p53 [110]	Inhibits apoptosis, supports survival
		AKT/Beclin1/VPS34/HIF-1α [112]	Impairs autophagy, enhances resistance to stress
	ADRB3	Epac/JNK/BDNF [26, 121]	Promotes neuronal recruitment and tumor progression
		Epac/JNK/mTOR [113]	Stimulates ribosome biogenesis, cell cycle entry
NGF	TrkA	MAPK/ERK [122]	Promotes tumor progression
		EphA2/SRC [57]	Promotes tumor progression
		HIF-1α [123]	Promote tumor new angiogenesis, promote tumor growth
BDNF	TrkB	ERK/MAPK [124, 125]	Promote cell proliferation, inhibit cell apoptosis and stimulate angiogenesis
		PI3K/AKT/mTOR [126, 127]	Regulates cell proliferation, growth, size, metabolism, and movement
		PLC-γ/DAG [128]	Increase the survival rate of tumor cells and promote invasion
		Jak/STAT [129, 130]	Increase the survival rate of tumor cells and promote invasion
	p75 NTR	NF-κB/MMP9 [131]	Promote tumor cell survival and metastasis
		AKT/ERK [132]	Promote tumor cell survival and metastasis
Glutamate	NMDAR	FMRP/HSF1 [119, 120, 133]	Promotes invasion and metastasis via translational regulation of stress response proteins
		CaMKII/MAPK/CREB, METTL3/m6A/HK2 [117, 118]	Enhances glycolysis, supports perineural invasion
	AMPAR	MAPK [134, 135]	Promotes invasion and migration in pancreatic cancer
		K-Ras/p38, K-Ras/p44/42[120]	Increases aggressiveness of precancerous lesions

[103]. In prostate cancer, acetylcholine released by parasympathetic nerve endings activates CHRM1 in mesenchymal stromal cells, promoting tumor proliferation and metastasis. Additionally, CHRM4 has been implicated in neuroendocrine differentiation, a critical step in prostate cancer progression. NGF-induced CHRM4 expression activates AKT signaling, which promotes cancer cell migration, invasion, and dissemination [54].

nAChRs are extensively involved in nerve-tumor interactions. Subunits such as α3, α4, α5, and α7 have been strongly associated with PDAC stem cell proliferation and resistance to inhibitory signals from neurotransmitters like GABA [104]. Selective knockdown of α2/β4nAChR inhibits GABA production in PDAC cell lines and benign pancreatic epithelial cells [105]. Recent studies also implicate the acetylcholine/CHRNA5 (α5-nAChR subunit) axis in promoting intrahepatic cholangiocarcinoma (ICC) metastasis. Acetylcholine binds CHRNA5, activating the Ca^{2+}-dependent CaMKII/GSK-3β/β-catenin signaling pathway. This pathway upregulates β-catenin expression, enhances neural infiltration by

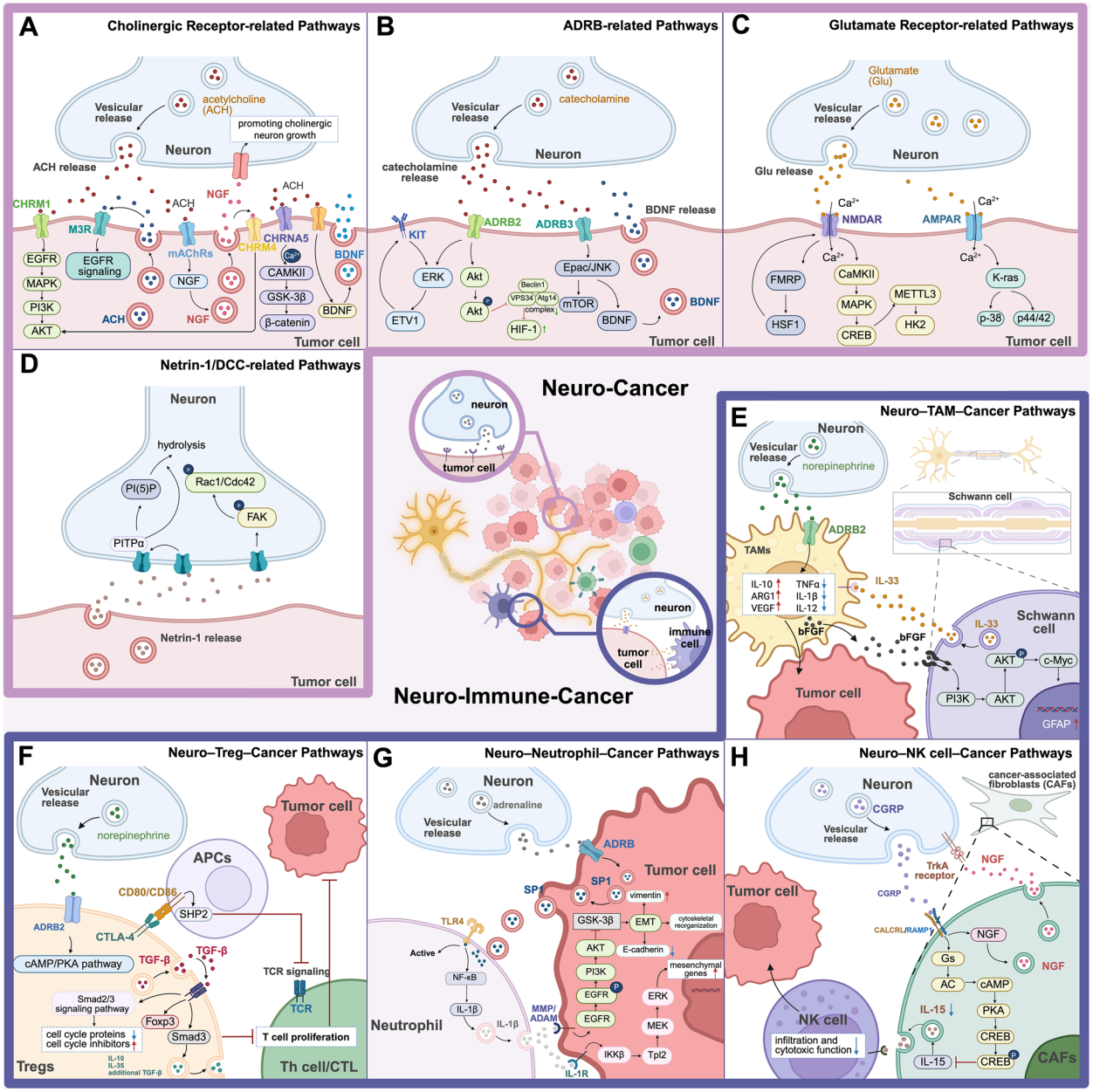


Fig. 4 Cancer-nervous system related pathway **A**. Cholinergic receptor-related pathways: CHRM1 activation suppresses EGFR/MAPK/PI3K/AKT signaling, inhibiting tumor progression. Conversely, tumor-derived acetylcholine activates M3R in an autocrine/paracrine manner, leading to EGFR transactivation and tumor proliferation. Cholinergic signaling also induces NGF expression, stimulating cholinergic nerve growth and forming a positive feedback loop. NGF upregulates CHRM4, activating AKT to promote invasion and metastasis. Acetylcholine binding to CHRNA5 triggers CaMKII/GSK-3β/β-catenin signaling, enhancing metastasis. **B**. Adrenergic receptor-related pathways: Neuronal signals activate ADRB receptors on tumor cells. ADRB2 promotes ETV1/c-KIT signaling via ERK and inhibits autophagy through AKT activation. ADRB3 promotes proliferation via Epac/JNK and mTOR pathways and stimulates BDNF release, enhancing neuronal support within the tumor microenvironment. **C.** Glutamate receptor-related pathways**.** Neuronal glutamate activates NMDAR on tumor cells, triggering calcium influx and downstream activation of FMRP/HSF1, CaMKII/MAPK pathways, promoting tumor growth and progression. Glutamate also activates AMPAR, inducing MAPK, K-ras signalings, further enhancing tumor proliferation. **D**. Netrin-1/DCC-related pathway: Tumor-secreted netrin-1 binds neuronal DCC receptors, inducing FAK, Rac1, and Cdc42 phosphorylation, promoting nerve fiber growth. It also recruits PITPα to DCC, enhancing PI(5)P hydrolysis and neurite extension. **E-H**. Neuro-immune-cancer pathways. **E**. Norepinephrine activates ADRB2 on TAMs, inducing IL-33 and M2 polarization. TAMs secrete bFGF, stimulating Schwann cells via PI3K/AKT and promoting perineural invasion. **F**. ADRB2 on Tregs induces cAMP/PKA signaling, enhancing Treg migration and suppressive function; TGF-β/Smad2/3 promotes Treg differentiation, inhibiting anti-tumor immunity. **G**. Adrenaline enhances tumor exosome release and SP1 expression, activating neutrophils to secrete IL-1β, which triggers EGFR/PI3K/AKT and MEK/ERK pathways, facilitating EMT and metastasis. **H**. CGRP from nociceptors activates CAFs via cAMP/PKA, reducing IL-15 and impairing NK cells. CGRP also increases NGF, reinforcing immunosuppression and neuroinvasion

increasing BDNF, and promotes both metastasis and drug resistance in ICC [43].

In conclusion, cholinergic receptors, particularly the M3R and α7-nAChRs, play integral roles in tumor progression by promoting proliferation, regulating inflammation, modulating the tumor microenvironment, and facilitating neuroinvasion. Targeting cholinergic signaling may offer promising therapeutic avenues in oncology.

Adrenergic receptors -related pathways

Beta-adrenergic receptors (ADRB), especially ADRB2 and ADRB3, are commonly found on the surface of various tumor cells and serve as critical mediators of neural influence on tumor biology. Under conditions of chronic stress, catecholamines such as norepinephrine are secreted by the sympathetic nervous system, activating ADRBs and modulating downstream signaling pathways involved in tumor progression. These downstream pathways serve as intermediaries through which the nervous system modulates tumors, bridging the influence between neurons and tumors (Fig. 4B).

ADRB2 is a principal mediator of catecholaminergic effects in tumors and plays a crucial role in the neural regulation of gastrointestinal stromal tumors (GIST). It promotes the ETS translocation variant 1 (ETV1)/c-KIT axis, a pathway essential for GIST development. ETV1, a lineage-specific transcription factor in GIST, facilitates tumorigenesis via MAPK-ERK signaling activated by ADRB2 stimulation [106–108]. Chronic restraint stress has been shown to trigger sustained catecholamine release, which promotes gastric epithelial transformation and carcinogenesis via ADRB2 signaling [109]. Local neuronal release of catecholamines also enhance AKT activation, promoting ubiquitination and degradation of p53, thereby inhibiting epithelial apoptosis and supporting tumor cell survival [110]. In addition, ADRB2-mediated upregulation of AKT disrupts the Beclin1/VPS34/Atg14 complex, impairing autophagy and stabilizing HIF-1α. This metabolic reprogramming enhances tumor cell resistance to hypoxia and other stressors, favoring survival in adverse microenvironments [111, 112]. Beyond ADRB2, ADRB3 contributes to neural-tumor communication under prolonged adrenergic stimulation. ADRB3 activation induces BDNF expression in tumor cells via an Epac (exchange protein activated by cAMP)/JNK (c-Jun N-terminal kinase)-dependent pathway. BDNF is subsequently secreted into the tumor microenvironment, where it supports further neuronal recruitment and plasticity. While the relationship between Epac and JNK in this context, whether cooperative or parallel, remains to be fully clarified, both are implicated in regulating BDNF-mediated tumor progression. Moreover, ADRB3 signaling engages the mammalian target of rapamycin (mTOR) pathway to stimulate ribosome biogenesis, thereby facilitating G0-G1 cell cycle progression and impeding differentiation into adipocyte-like phenotypes [113]. In summary, ADRB2 and ADRB3 are central mediators of adrenergic signaling in tumors. By regulating cell proliferation, metabolic adaptation, immune evasion, and neural remodeling, these receptors constitute promising targets for therapies aimed at disrupting the neural regulation of tumor progression.

Glutamate receptor-related pathways

Glutamate, a key excitatory neurotransmitter, is predominantly active within the central nervous system (CNS), where it plays a crucial role in synaptic transmission and neuronal plasticity. Its receptors, including NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), are essential mediators of CNS functions such as learning, memory, and neural communication [114–116]. Interestingly, emerging evidence suggests that glutamate also exerts regulatory effects beyond the CNS, particularly on peripheral tumors such as PDAC. These effects are mediated through the glutamate receptors expressed on tumor cells, including NMDAR and AMPAR, suggesting a potential role for glutamate signaling in cancer biology [117–120] (Fig. 4C).

One mechanistic link involves guanylate kinase-associated protein (GKAP), a scaffold protein of NMDARs, promotes fragile X mental retardation protein (FMRP)/heat shock factor 1 (HSF1) signaling, which collectively drives tumor invasion and malignancy. Calcium influx through NMDARs enhances FMRP translation, and although the exact mechanism remains unclear, strong associations have been identified in candidate gene studies. FMRP binds HSF1 mRNA, promoting its translation and phosphorylation at serine 326, thereby activating HSF1. Intriguingly, FMRP also binds mRNAs encoding NMDAR subunits (GluN1, GluN2 A, GluN2B), suggesting a positive feedback loop that amplifies NMDAR signaling. Their reciprocal regulation appears complex and bidirectional, requiring further investigation [119]. In parallel, NMDAR-mediated calcium influx activates the CaMKII/MAPK pathways. This activation results in phosphorylation of CREB at Ser133, enhancing its transcriptional activity [118]. Notably, CREB activation induces Methyltransferase Like 3 (METTL3) expression, which upregulates hexokinase 2 (HK2) via N6-methyladenosine (m6A) mRNA modification, enhancing glycolysis and promoting PNI in tumor cells [117]. These pathways have been validated in mouse models of PDAC. Glutamate-mediated AMPAR activation in PDAC promotes tumor progression via the MAPK/K-ras pathway, supported by in vitro studies, while in vivo evidence

remains limited [120] (Fig. 4C). These insights underscore the intricate role of glutamate receptor-related pathways in mediating neural modulation of tumor behavior, highlighting its potential as a therapeutic target in cancer treatment.

Netrin-1/DCC-related pathways

Netrin-1, a well-characterized neurotrophic factor, plays essential roles in the development of the central nervous system, spinal cord, and peripheral nerves. Beyond its physiological functions, it is increasingly recognized as a key modulator in tumor biology, particularly in relation to tumor-associated pain. Elevated expression of Netrin-1 within the tumor microenvironment activates specific neuronal receptors and initiates downstream signaling cascades that promote neural innervation of tumors, thereby contributing to the onset and persistence of cancer-related pain [136]. Emerging evidence highlights a strong association between Netrin-1 expression and tumor aggressiveness. Its upregulation has been documented across a broad range of malignancies, where it facilitates tumor-nerve interactions. Tumors may exploit Netrin-1 signaling to modulate neuronal activity, which in turn regulates both tumor behavior and immune responses [136, 137]. This bidirectional communication between the nervous system and tumors creates a mutually supportive environment that enhances tumor survival, progression, and pain generation (Fig. 4D).

DCC, a transmembrane receptor primarily expressed on neurons, serves as a principal receptor for Netrin-1. Activation of DCC has been shown to direct axonal growth through specific intracellular pathways. In models of bone cancer, DCC-mediated signaling contributes to increased innervation by $CGRP^+$ sensory nerve fibers, exacerbating nociceptive signaling and cancer-induced bone pain [138]. When DCC on neurons is attracted and activated by Netrin-1 from cancer cells, it promotes phosphorylation of focal adhesion kinase (FAK) and subsequently Rac family small GTPase 1/cell division cycle 42 (Rac1/Cdc42) signaling pathway. This Netrin-1/DCC/FAK/Rac1/Cdc42 axis drives the sprouting and elongation of peripheral $CGRP^+$ nerve fibers, thereby enhancing nociceptive innervation during cancer pain progression [139]. These findings suggest that activation of the Netrin-1/DCC pathway in the tumor milieu facilitates neuroplastic changes that amplify pain perception. In addition to its role in nociceptive innervation, Netrin-1 also promotes axonal outgrowth through another mechanism involving phosphatidylinositol transfer protein-α (PITPα). Upon stimulation by Netrin-1, PITPα is recruited to the plasma membrane via interaction with DCC, which may induce conformational changes that enhance hydrolysis of phosphatidylinositol 5-phosphate (PI(5)P). This process likely contributes to axon elongation and may further promote local PI(5)P synthesis, reinforcing the signaling cascade. Although the full role of the Netrin-1/DCC/PITPα/PI(5)P pathway in the context of tumor-nerve interactions remain to be fully elucidated, it presents a promising mechanism by which tumors may hijack neuronal growth processes.

Importantly, Netrin-1 not only functions as a common neurotrophic factor guiding neuronal growth but also critically determines neuronal survival. Studies have shown in regions of the nervous system where local Netrin-1 is absent, axonal terminals and growth cones undergo morphological collapse reminiscent of apoptosis. This effect may not result solely from lack of downstream pathway activation but could also involve the unliganded DCC receptor, which has been suggested to exert pro-apoptotic effects in the absence of Netrin-1 binding. This mechanism, however, remains hypothetical and warrants further investigation [140].

In summary, Netrin-1/DCC signaling pathways are central to both normal neuronal development and pathological processes associated with cancer, particularly tumor-induced neuroplasticity and pain. Elucidating these mechanisms enhances our understanding of the tumor-nervous system interface and may inform novel therapeutic strategies aimed at alleviating cancer-related neurological complications.

Neuro-immune-cancer pathways

Neuronal activity has been increasingly recognized as a modulator of immune system function, which in turn plays a pivotal role in tumor development and progression. The immune system serves as a critical intermediary in the bidirectional communication between the nervous system and tumors, facilitating indirect neurotumoral interactions. Neural influences on immune cells may impair their ability to detect and eliminate tumor cells, thereby fostering tumor immune evasion. Consequently, the nervous system, via its regulation of immune components, can enhance tumor growth, progression, and metastasis. The following sections categorize these regulatory interactions according to immune cell types involved (Table 3).

Tumor-Associated Macrophages (TAMs)

TAMs are integral components of the tumor microenvironment (TME), and their phenotypes are dynamically regulated by neural signals [141, 142] (Fig. 4E). In particular, sympathetic nervous system activity modulates TAM behavior through the release of norepinephrine, which binds to β2-adrenergic receptors (ADRB2) on TAMs. This interaction promotes the expression of immunosuppressive and pro-tumorigenic factors such as

Table 3 The changes in immune cells within the tumor immune microenvironment influenced by the nervous system

Immune cell types	Mechanism of action of the nervous system	Changes in immune cells	Effects on tumors	Key molecule
Tumor-Associated Macrophages (TAMs) [141]	Activate ADRB2 on tams [143]	Upregulate immunosuppressive molecules, pro-angiogenic VEGF [144], suppress pro-inflammatory cytokines	Impaire antitumor immunity, drive tumor progression [145]	IL-10↑, ARG1↑, VEGF↑, TNFα↓, IL-1β↓, IL-12↓
	Activate Schwann cells, upregulate GFAP	Activate Schwann cells, polarize into M2 tumor-promoting phenotypes, form a TAM-Schwann cell positive feedback loop	Accelerate tumor metastasis [146]	GFAP↑
	Secrete NGF, activate the TrkA receptor	Trigger PI3K/AKT pathway, promote mTOR activation, increase VEGF and IL-6	Enhance angiogenesis and tumor cell survival [161]	VEGF↑, IL-6↑
	Secrete GDNF, activate the RET tyrosine kinase receptor	Regulate tumor cell metabolic reprogramming, cytoskeletal dynamics, and microenvironmental adaptation	Promote tumor cells' migration enhances perineural invasion capabilities [162]	GDNF↑
Regulatory T Cells (Tregs)	Activate the camp/PKA pathway in Tregs, promote their migration into the tumor microenvironment	Suppress T-cell proliferation, downregulate cyclin D/E, upregulate p21/p27	Suppress the antitumor immune response, enhance their own proliferation, reinforce immunosuppression, facilitate tumor immune evasion [151]	TGF-β↑, cell cycle proteins↓, cell cycle inhibitors↑
	Activate the cAMP/PKA pathway in Tregs, promote their migration into the tumor microenvironment	Activating Foxp3, drive naïve $CD4^+$ T-cell differentiation into immunosuppressive iTregs	Suppress the antitumor immune response, enhance their own proliferation, reinforce immunosuppression, facilitate tumor immune evasion [151]	TGF-β↑, Foxp3↑
	Activate the cAMP/PKA pathway in Tregs, promote their migration into the tumor microenvironment	Amplify by inducing IL-10, IL-35, and TGF-β secretion, form a self-reinforcing immunosuppressive loop	Suppress the antitumor immune response, enhance their own proliferation, reinforce immunosuppression, facilitate tumor immune evasion [151]	IL-10↑, IL-35 ↑, TGF-β↑
	Activate the cAMP/PKA pathway in Tregs, promote their migration into the tumor microenvironment	Bind CD80/CD86 on APCs, recruite SHP2 phosphatase, inhibit TCR signaling and block T-cell activation, reinforce immune suppression	Suppress the antitumor immune response, enhance proliferation, reinforce immunosuppression, facilitate tumor immune evasion [151]	SHP2 phosphatase↑
	Release NE, activate the β2-adrenergic receptor (β2-AR)	Trigger the camp-PKA signaling pathway, promote the secretion of IL-10 and TGF-β	Inhibit effector T cell activity, suppress anti-tumor immune responses [163]	IL-10↑, TGF-β secretion↑
Neutrophils	Undergo enhanced production and modification, increase SP1 levels, facilitate neutrophil activation, secrete IL-1β	Activate MMP/ADAM proteases, release EGFR ligands, trigger EGFR-PI3K/AKT signaling [155], inhibit GSK-3β, stabilize EMT transcription factor, downregulate E-cadherin, upregulate vimentin, enhance cell motility	Enable superior adaptation to metastatic microenvironments, potentiate the metastatic capacity of cancer cells [157]	IL-1β↑, EGFR↑
	Undergo enhanced production and modification, increase SP1 levels, facilitate neutrophil activation, secrete IL-1β	Bind to IL-1R, activate the MEK/ERK pathway [156], induce the expression of mesenchymal genes, enhance cell migration and invasion capabilities	Enable superior adaptation to metastatic microenvironments, potentiate the metastatic capacity of cancer cells [157]	IL-1β↑
	Secrete SPP1, release catecholamines by sympathetic nerves, enhance CXCL1 secretion, CXCL1 binds to the CXCR2 receptor	SPP1 binds to neutrophil surface receptor, activate the ERK pathway, promote NET formation; nets capture circulating tumor cells, release inflammatory mediators	Promote tumor cell survival and invasion [164]	SPP1↑, inflammatory mediators↑

Table 3 (continued)

Immune cell types	Mechanism of action of the nervous system	Changes in immune cells	Effects on tumors	Key molecule
Natural Killer (NK) Cells	Release CGRP, bind to the CGRP receptors RAMP1 and CALCRL, activate AC, elevate intracellular camp levels, stimulate PKA [158]	Phosphorylate the transcription factor CREB, suppress IL-15 [159]	Drive tumor progression, exacerbate cancer-related pain, promote PDAC aggressiveness and pain hypersensitivity [160]	CGRP↑, IL-15↓
	Release CGRP, bind to the CGRP receptors RAMP1 and CALCRL, activate AC, elevate intracellular camp levels, stimulate PKA [158]	Secret NGF, bind to the TrkA receptor, enhance CGRP release, establish a self-reinforcing feedback loop	Drive tumor progression, exacerbate cancer-related pain, promote PDAC aggressiveness and pain hypersensitivity [160]	CGRP↑
	Induce tumor cells or antigen-presenting cells to express PD-L1	Bind to the PD-1 receptor, activate downstream inhibitory signaling pathways, suppress the PI3K/AKT/mTOR pathway, reduce the synthesis and release of cytotoxic granules	Suppres anti-tumor immunity [165]	PD-L1↑, cytotoxic granules↓

interleukin-10 (IL-10), arginase 1 (ARG1), which inhibits T cell metabolism [143], and vascular endothelial growth factor (VEGF, which promotes angiogenesis) [144]. Simultaneously, norepinephrine suppresses TAM production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-12, thereby weakening anti-tumor immune responses and facilitating tumor progression [145]. Moreover, TAMs secrete basic fibroblast growth factor (bFGF), which binds to bFGF receptors on Schwann cells, activating the PI3K-Akt signaling pathway. Akt then phosphorylates and activates c-Myc, which translocates to the nucleus to upregulate glial fibrillary acidic protein (GFAP), a marker of Schwann cell activation. These activated Schwann cells promote PNI by increasing migration and secreting interleukin-33 (IL-33), which recruits additional macrophages and further induces M2 polarization. This positive feedback loop between TAMs and Schwann cells plays a central role in the neural invasion and metastatic behavior of PDAC [146]. Overall, interactions between neurons, glial cells, and TAMs, whether through neural modulation of cytokine profiles or reciprocal activation loops, serve to suppress anti-tumor immunity while enhancing tumor progression and dissemination.

Regulatory T Cells (Tregs)

Tregs in the tumor microenvironment predominantly exhibit immunosuppressive effects against anti-tumor immunity [147]. With advancing research, increasing evidence suggests that this suppression is intricately linked to neural mechanisms. Specifically, the nervous system regulates the proliferation, metabolism, and immunosuppressive functions of Tregs through neurotransmitters, nerve fiber infiltration, and neuro-immune signaling pathways, thereby promoting tumor immune evasion [148]. Sympathetic nerve-released norepinephrine also influences the behavior of regulatory T cells (Tregs) by activating the cAMP/PKA signaling pathway through β2-adrenergic receptors. This enhances Treg migration into the TME, where they execute potent immunosuppressive functions (Fig. 4F). Tregs inhibit anti-tumor immunity through multiple mechanisms: On the one hand, Tregs secrete TGF-β, which downregulates cell cycle proteins (e.g., cyclin D/E) and upregulates cell cycle inhibitors (e.g., p21, p27) via the Smad2/3 signaling pathway, inducing G1 phase arrest and inhibiting T cell proliferation [149]. Besides, TGF-β activates Foxp3, a key transcription factor in Tregs, driving the differentiation of naive $CD4^+$ T cells into induced Tregs (iTregs). TGF-β also further amplifies immunosuppression through Smad3 signaling, promoting Treg secretion of IL-10, IL-35, and additional TGF-β [150], which forms a positive feedback loop. On the other hand, Tregs express high levels of CTLA-4, which binds to CD80/CD86 on antigen-presenting cells (APCs), leading to recruitment of the SHP2 phosphatase, suppression of TCR signaling, and blockade of T cell activation [151]. Through these pathways, Tregs not only dampen anti-tumor immune responses but also promote their own expansion, thereby reinforcing immune suppression and facilitating tumor immune evasion [151].

Neutrophils

Neutrophils are often regarded as a "double-edged sword" in anti-tumor immunity, exhibiting distinct roles across different tumor microenvironments [152]. The nervous system significantly modulates the dual roles of neutrophils in tumor progression, both pro-tumorigenic and anti-tumorigenic, through neurotransmitter release, microenvironment remodeling, and direct cellular interactions [153, 154] (Fig. 4G). Under chronic stress conditions, chronic stress affects the activity of the sympathetic nervous system and activates β-adrenergic receptors on tumor cells, which induces the increased SP1 levels in tumor-derived exosomes (TDES) facilitate neutrophils activation by binding to TLR4 on neutrophils and activates the TLR4/NF-κB signaling pathway, leading to IL-1β secretion of neutrophils. Subsequently, IL-1β promotes cancer metastasis via coordinated activation of both EGFR-dependent PI3K/AKT and IL-1R-dependent MEK/ERK signaling pathways in cancer cells [155, 156].

As for the EGFR-dependent PI3K/AKT pathways, IL-1β activates Matrix metalloproteinase (MMP)/ADAM proteases to release EGFR ligands, resulting in EGFR phosphorylation and subsequent PI3K/AKT pathway activation. This pathway inhibits GSK-3β activity to stabilize EMT transcription factors, which subsequently downregulates E-cadherin expression, promotes cytoskeletal reorganization, and upregulates vimentin expression, finally leads to the enhancement of cell motility and result in promoting cancer metastasis. Meanwhile, IL-1β can also directly binds to IL-1R on tumor cells and activates the MEK/ERK pathway through the IKKβ/Tpl2 cascade, inducing the expression of mesenchymal genes and enhancing cell migration and invasion capabilities.

This dual-pathway synergistic mechanism originated from IL-1β secreted by neutrophils under the influence of neuroendocrine exosomes drives epithelial cells to retain partial epithelial markers through incomplete E-cadherin loss while simultaneously gaining mesenchymal characteristics via vimentin upregulation, thereby establishing a hybrid epithelial-mesenchymal phenotype. Such phenotypic plasticity enables superior adaptation to metastatic microenvironments and ultimately potentiates the metastatic capacity of cancer cells [157].

Natural Killer (NK) cells

NK cells are key effectors in anti-tumor immunity. However, their function can be suppressed through neuro-immune interactions within the TME (Fig. 4H). In the TME of PDAC, nociceptor neurons release CGRP, which binds to the CGRP receptors RAMP1 and CALCRL on the surface of cancer-associated fibroblasts (CAFs). Upon receptor binding, CGRP activates adenylate cyclase (AC) via the Gs protein, elevating intracellular cAMP levels and stimulating PKA [158]. The cAMP/PKA pathway phosphorylates the transcription factor CREB, leading to transcriptional suppression of IL-15, a critical cytokine for the survival, proliferation, and activation of NK cells [159]. As a result, reduced IL-15 levels impair NK cell recruitment and effector function, compromising tumor immunosurveillance. Meanwhile, CGRP-stimulated CAFs secrete NGF, which activates TrkA receptors on nociceptor neurons, further enhancing CGRP release. This positive feedback loop exacerbates both immune suppression and nociceptor sensitization. This neuro-immune interplay not only facilitates immune evasion by suppressing NK cell activity but also contributes to neural remodeling and cancer pain, thereby promoting PDAC aggressiveness and hypersensitivity [160].

Implication of targeting neural-cancer interactions

The increasing recognition of neuro-tumor interactions has highlighted the pivotal role of the nervous system in tumor initiation, progression, and metastasis. Advancements in this area, supported by accumulating preclinical and translational studies, have unveiled novel therapeutic targets and strategies. Both pharmacological and non-pharmacological interventions are now being explored to modulate these interactions. A growing body of evidence supports the development of therapies aimed at disrupting neural inputs that facilitate tumor development, thus offering potential avenues to modulate disease progression. Moreover, several non-invasive therapies have already been translated into clinical practice, underscoring their therapeutic promise and clinical relevance.

Drug therapies targeting the neurobiology of cancer

Targeting nervous system to inhibit tumor growth and metastatic spread

From a microscopic perspective, neuronal secretion of cell adhesion molecules, neurotrophic factors, and neurotransmitters can regulate tumor growth and metastasis, making the modulation of neuronal secretion a potential anti-tumor strategy (Fig. 5A-C, Table 4). As previously discussed, cholinergic receptor signaling mediated by acetylcholine is essential in driving cancer proliferation, invasion, and metastasis. Both pharmacological inhibition and genetic knockout of the muscarinic acetylcholine M3 receptor have shown inhibitory effects on gastric, small intestine, and breast tumors. Botulinum toxin (BoNT), which blocks acetylcholine release, has also been shown to suppress tumor growth, suggesting a functional link between acetylcholine signaling and cancer progression, although the precise mechanism remains to be fully elucidated [166] (Fig. 5A).

Glutamatergic signaling also plays a key role in neuro-tumor communication. mGluR1, a metabotropic glutamate receptor, is required to maintain a tumorigenic phenotype, as shown by inducible RNA silencing systems. For instance, treatment of Michigan Cancer Foundation-7 (MCF-7) xenografts with the glutamate release inhibitor riluzole resulted in significant suppression of tumor progression [167, 168] (Fig. 5B). Neurotrophic factors such as BDNF and NGF further drive tumor growth by activating Trk receptors on tumor cells. Trk inhibitors like larotrectinib and entrectinib have shown significant and sustained efficacy in clinical trials, although resistance remains a challenge; next-generation Trk inhibitors are currently under development to address this issue [169] (Fig. 5C).

Denervation studies provide additional evidence for the contribution of the nervous system to tumor progression. Zhao et al. demonstrated that surgical vagotomy or localized BoNT-A injection significantly reduced tumor development in three distinct gastric cancer mouse models [14]. Likewise, Magnon et al. reported that both chemical and genetic ablation of β2- and β3-adrenergic signaling suppressed prostate tumor growth and metastasis in murine models [12]. Notably, optogenetic stimulation of the optic nerve has been shown to initiate gliomagenesis, whereas sensory deprivation (e.g., dark rearing) inhibited tumor development in vivo, highlighting the importance of neural activity in tumor initiation [170].

Despite compelling evidence from animal models, translation to human cancer therapy requires further investigation. Many neural-targeting interventions exhibit only transient efficacy, with tumors eventually adapting and circumventing these pathways. Thus, strategies that target neural influences must be integrated into broader, multimodal treatment approaches to achieve durable clinical benefits.

Remodeling the immune system via neural modulation for cancer therapy

The immune system also serves as a vital mediator in the interaction between the nervous system and tumors (Fig. 5D-F, Table 4). Neural regulation within the tumor microenvironment can dampen immune surveillance and promote tumor immune evasion. Therefore, targeting neural-immune crosstalk represents a promising strategy

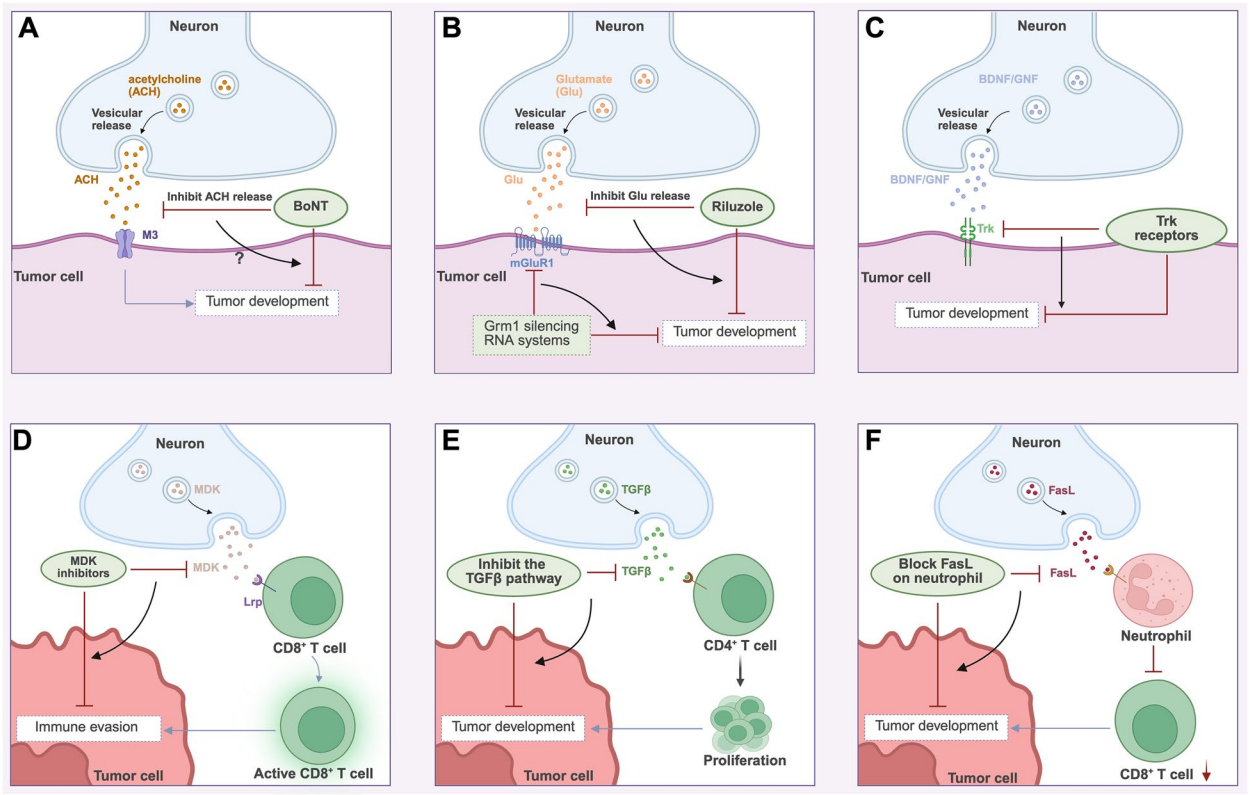


Fig. 5 Implication targeting neural-cancer interaction: **A**. Botulinum toxin (BoNT) may inhibit tumor progression by suppressing neuronal acetylcholine release. **B**. An induced Grm1 silencing RNA system can block mGluR1, disrupting glutamate-mediated neural influences in the tumor microenvironment and exerting antitumor effects. Riluzole, a glutamate release inhibitor, has been shown to suppress breast cancer progression. **C**. Trk inhibitors can suppress neuron-secreted neurotrophic factors such as BDNF and GNF, which promote tumor development by binding to Trk receptors on tumor cells. **D**. MDK inhibitors can block neuron-mediated $CD8^+$ T-cell activation via MDK secretion, thereby preventing tumor immune evasion. **E**. Inhibiting the TGF-β pathway may suppress neuronal secretion of TGF-β, which otherwise promotes $CD4^+$ T-cell proliferation and contributes to cancer progression. **F**. Blocking FasL interactions with neutrophils can reverse FasL-induced immunosuppressive effects on tumor-specific $CD8^+$ T cells, thereby inhibiting tumor growth and progression

not only for tumor control but also for addressing tumor-induced neurological complications.

Neurons can influence immune cells through several mechanisms. For example, secretion of MDK can activate $CD8^+$ T cells in a manner that paradoxically promotes immune evasion. In vitro studies by Liu et al. showed that MDK inhibitors enhanced the efficacy of immune modulators in ovarian cancer cells [171] (Fig. 5D). Neurons also secrete TGF-β to stimulate $CD4^+$ T cell proliferation and produce Fas ligand (FasL) to induce T cell apoptosis [172, 173]. In basal-like breast cancer (BLBC), low TGF-β activity correlates with heightened $CD4^+$ T cell function and reduced recurrence, suggesting that inhibition of TGF-β signaling could enhance immunotherapeutic outcomes [174]. These data indicate that inhibiting the TGFβ pathway may serve as a promising therapeutic strategy to boost the immune system's efficacy in treating BLBC (Fig. 5E). Fas is a crucial factor in tumor immunotherapy. Shan et al. found that overexpressing FasL enabled neutrophils to acquire immunosuppressive functions against tumor-specific $CD8^+$ T cells, promoting the growth and progression of human gastric cancer cells both in vitro and in vivo. This effect could be reversed by blocking FasL on these neutrophils [175] (Fig. 5F).

The nervous system also exerts regulatory effects directly within tumor cells. For instance, Wang et al. demonstrated that blocking acetylcholine signaling with the receptor antagonist 4-DAMP reduced PD-L1 expression and self-renewal in $CD133^+$ thyroid cancer cells [29]. In a related pathway, the neurotransmitter GABA, acting through $GABA_B$ receptors on tumor cells, has been shown to impair T cell infiltration. Sun et al. found that combining the $GABA_B$ receptor agonist baclofen with anti-PD-L1 therapy enhanced immune response and tumor suppression in a breast cancer mouse model [176]. Collectively, these findings highlight the therapeutic

Table 4 Drugs targeting the Cancer-nervous system

Drug Name	Mechanism of Action	Cancer Type	Drug Type	Research Stage
Propranolol [177]	Blocks β2 receptors, inhibits sympathetic signaling, reduces inflammatory cytokines and pro-metastatic molecules	Breast cancer	β2-adrenergic receptor antagonist	Preclinical research
Carvedilol [178]	Blocked the effects of sympathetic nervous system activation	Breast cancer	β-adrenergic receptor antagonist	Retrospective clinical studies
Atenolol [179]	Inhibits sympathetic nerve-driven metabolic reprogramming to reduce tumor proliferation	Breast cancer	β1-adrenergic receptor antagonist	Preclinical research
Tiotropium [180]	Binds to M3 receptor to form a complex	Lung cancer	M3 muscarinic receptor antagonist	Retrospective clinical studies
Atropine [181]	Attenuates immunosuppressive markers and M3R via inhibition of EGFR/AKT/ERK signaling pathways	Colorectal cancer	Non-selective M1-M5 antagonist	Preclinical research
Larotrectinib [182]	Targets NTRK fusion genes, blocks MAPK/ERK and PI3K/AKT pathways	NTRK fusion-positive solid tumors (e.g., Sarcoma)	TrkA/B/C inhibitor	Preclinical research
Entrectinib [182]	Inhibits Trk signaling and perineural invasion	NTRK fusion-positive solid tumors (e.g., Lung cancer)	Trk/ROS1/ALK inhibitor	Preclinical research
Selitrectinib [169]	Overcomes Trk kinase domain mutations	Trk kinase domain mutation-resistant tumors	Second-gen Trk inhibitor	Preclinical research
Repotrectinib [183]	Penetrates blood-–brain barrier to suppress intracranial metastasis	Breast cancer brain metastasis	Trk/ROS1/ALK inhibitor	Preclinical research
Cabozantinib [184, 185]	Decreases proliferation and migration of osteosarcoma cells, inhibiting ERK and AKT signaling pathways	Osteosarcoma	TrkB/MET/VEGFR2 inhibitor	Phase II clinical trial
SR48692 [186]	Inhibits MAPK/ERK, PI3K/AKT, and PKC pathways to suppress tumor proliferation	Pancreatic cancer	Neurotensin receptor (NTSR1) antagonist	Preclinical research
Naltrexone [177, 187]	Activates TLR4 signaling to enhance immunity and induce apoptosis	Pancreatic cancer, breast cancer	Non-selective opioid antagonist (low-dose)	Preclinical research
MDK inhibitor (iMDK) [171]	Inhibits MDK-mediated $CD8^+$ T cell suppression	Ovarian cancer	Small molecule inhibitor	Preclinical research
TGFβ inhibitor [174]	Blocks TGFβ signaling to enhance $CD4^+$ T cell activity	Basal-like breast cancer	Small molecule/antibody	Preclinical research
FasL blocker [175]	Blocks FasL-mediated T cell apoptosis	Gastric cancer	Antibody	Preclinical research
Baclofen [176]	$GABA_B$ receptor agonist; stabilizes PD-L1	Breast cancer	Small molecule agonist	Preclinical research

potential of targeting neuro-immune interactions to enhance anti-tumor immunity. However, while immunotherapy has revolutionized cancer treatment, its efficacy remains variable, necessitating further refinement and the development of new immunotherapies specifically designed to disrupt neural-tumor immune pathways.

Non-invasive, non-pharmacological approaches related to the neurobiology of cancer

While pharmacological approaches targeting neural-cancer interactions have shown considerable promise, their clinical application is often limited by serious side effects, such as chemotherapy-induced peripheral neuropathy (CIPN) and neurotoxicity associated with immune

checkpoint inhibitors (ICIs) [188, 189]. In recent years, non-invasive, non- pharmacological interventions have gained attention for their ability to prevent cancer progression, enhance the efficacy of existing treatments, and improve patient quality of life without inducing significant adverse effects [190–192].

Accumulating evidence over the past decade has established a clear link between psychological stress and cancer progression. These effects are largely mediated by the sympathetic-adrenal-medullary (SAM) axis and its catecholaminergic outputs, such as norepinephrine and epinephrine. These stress mediators promote tumor progression by stimulating cancer cell proliferation, angiogenesis, and motility; inhibiting cytotoxic immune cell activity; and enhancing the tumor-promoting functions of immune-suppressive cells. Furthermore, stress-induced sympathetic signaling has been shown to diminish the effectiveness of conventional treatments, including surgery, chemotherapy, radiotherapy, and immunotherapy [193]. Consequently, stress management and psychological interventions are now considered critical components of comprehensive cancer care. Psychotherapeutic strategies, particularly those targeting neuroendocrine stress responses, have demonstrated the ability to modulate sympathetic output, reduce excessive adrenergic signaling, and enhance immunochemotherapeutic efficacy [193, 194]. Among these, Cognitive Behavioral Therapy (CBT) has shown significant benefit. A meta-analysis that included 13 controlled trials revealed that CBT substantially improved psychological resilience in cancer patients [195]. Similarly, mindfulness-based and positive psychology interventions, which encourage present-moment awareness and nonjudgmental acceptance, have demonstrated efficacy in reducing distress and improving emotional well-being. A meta-analysis of 21 clinical studies confirmed their effectiveness in alleviating psychological burden among cancer survivors [196, 197].

Behavioral interventions such as regular exercise, meditation, and yoga have emerged as adjunctive therapies with neurobiological benefits relevant to cancer care. These activities are thought to modulate autonomic nervous system balance, particularly by enhancing vagal tone. Increased vagal activity has been associated with elevated BDNF levels, TrkB pathway activation, improved neurogenesis, and synaptic plasticity, all of which contribute to neuroimmune regulation and possibly tumor inhibition [198]. Importantly, vagal activity can be non-invasively assessed through heart rate variability (HRV), a biomarker of autonomic function. Higher HRV is associated with improved cancer prognosis, including lower tumor marker levels and reduced mortality. HRV biofeedback (HRV-B), a method involving slow, rhythmic breathing combined with visual feedback, can enhance vagal tone and suppress sympathetic activity. This not only improves immune responses, such as increased natural killer (NK) and $CD8^+$ T cell activity, but may also reduce oxidative stress and tumor-promoting signaling within the tumor microenvironment [199]. These findings suggest that autonomic regulation through behavioral strategies may offer a safe, effective, and low-cost avenue for improving outcomes in cancer patients. Further investigation into the neurobiological mechanisms underlying these effects may help integrate such interventions more fully into standard oncology care.

Acupuncture and electroacupuncture (EA), cornerstone therapies in traditional Chinese medicine, have demonstrated efficacy in alleviating cancer-related symptoms, mitigating treatment side effects, and reducing cancer-related pain [200, 201]. Mechanistically, these therapies may activate mechanoreceptors and initiate afferent signaling through the ventrolateral fasciculus to specific brain nuclei. This activates descending pain inhibitory pathways involving endogenous opioid peptides, serotonin (5-HT), and other neurotransmitters [200]. Reflecting growing clinical support, the American Society of Clinical Oncology and the Society for Integrative Oncology issued a 2022 guideline recommending acupuncture or acupressure for the management of general cancer pain [202]. Notably, the IMPACT randomized controlled trial by Epstein et al. found that acupuncture combined with massage significantly alleviated pain and co-occurring symptoms (fatigue, insomnia) in patients with advanced cancer [203]. Transcutaneous electrical acupoint stimulation (TEAS), a non-invasive alternative to traditional acupuncture that uses surface electrodes, has also demonstrated efficacy in clinical settings. TEAS has been effective in relieving both acute and chronic postoperative pain in breast cancer patients, improving serum protein levels, and accelerating postoperative recovery in colorectal cancer cases In a study by Tian et al., TEAS significantly reduced postoperative pain scores in pancreatic cancer patients from day 1 to 4 post-surgery, reinforcing the analgesic potential of acupuncture-based modalities [204].

Compared with traditional therapies, which often suffer from drug side effects and limited efficacy of surgical methods, non-invasive and non-pharmacological therapies such as psychological interventions, behavioral therapy, and acupuncture offer several advantages: safety, accessibility, cost-effectiveness, and the potential to improve both tumor control and quality of life [193]. Crucially, many of these therapies exert their effects by modulating nervous system activity, thereby offering unique opportunities for integration into the emerging field of cancer neuromodulation. Future interdisciplinary

research combining oncology, neurology, immunology, and behavioral science is essential to further elucidate these mechanisms and optimize such interventions. This integrated approach holds significant promise for enhancing survival and long-term well-being in cancer patients.

Conclusions and perspectives

Historically, the role of the nervous system in tumorigenesis, progression, and metastasis has been largely overlooked. However, recent advancements in cancer neurobiology have highlighted the central involvement of neural mechanisms in oncogenesis. Over the past decade, this emerging field has gained substantial traction, demonstrating that neural regulation plays a pivotal role in at least five of the eight hallmarks and two enabling characteristics of cancer. Cancer development induces local nerve remodeling, and nerve growth with secreted factors introduces novel dynamics in cancer tissue proliferation and invasion, resulting in a self-perpetuating cycle that escalates the complexity and peril of tumor progression [205]. Neurotrophic factors and neurotransmitters serve as the intermediaries in the crosstalk between cancer and the nervous system [68]. Elevated expression levels of neurotrophic factors in tumor cells can stimulate the ingrowth of nerves within the tumor microenvironment and modulate neuronal excitability [71, 206]. Furthermore, the nervous system exerts its influence on tumors primarily through the regulation of the immune system, hormonal levels, and electrical signaling. Recent studies have evidenced that central nervous system stress can disrupt leukocyte trafficking and the secretion of inflammatory cytokines [207, 208]. Beyond the secretion of neurotrophic factors, the neuron-like alterations in cancer cells present a compelling feature of the tumor's regulation of the nervous system [209]. Tumor aggressiveness is significantly associated with the neuron-like synapses of cancer cells. Tumor cells are capable of forming tumor-neuron synapses with neurons. Upon metastasis to the brain, breast cancer cells can engage with neuronal synapses, creating pseudotriadic synapses that foster tumor proliferation [210].

In conclusion, the intricate crosstalk between the nervous system and cancer has opened new and promising avenues for therapeutic intervention. Nevertheless, several challenges must be addressed to translate these findings into clinical practice. First, the lack of a clear distinction between cancer-associated nerves and normal neural tissues presents a major obstacle in designing targeted therapies that avoid off-target effects. Second, although animal models suggest that surgical or genetic denervation can suppress tumor growth and metastasis, it remains uncertain whether pharmacological neural blockade can replicate these effects safely and effectively. Third, the potential for integrating neuromodulatory strategies with existing cancer therapies, such as immunotherapy or chemotherapy, requires systematic evaluation to determine synergistic benefits. Future research should aim to delineate the molecular and functional differences between normal and cancer-associated nerves, establish reliable biomarkers for neural involvement in cancer, and explore multimodal treatment paradigms targeting both the tumor and its neural environment. A deeper understanding of cancer neurobiology will not only advance our knowledge of tumor pathophysiology but also facilitate the development of innovative, mechanism-based therapies that harness the nervous system as a therapeutic ally.

Abbreviations

ADRB	Beta-adrenergic receptors
AKT	Ak strain transforming
AMPAR	α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor
BDNF	Brain-Derived Neurotrophic Factor
BoNT	Botulinum toxin
CCL2	C-C motif chemokine ligand 2
CCL4	C-C motif chemokine ligand 4
CCL5	C-C motif chemokine ligand 5
CGRP	Calcitonin gene-related peptide
CHRM1	cholinergic receptor muscarinic 1
CHRM3	cholinergic receptor muscarinic 3
CHRM4	cholinergic receptor muscarinic 4
CHRNA5	α5 nAChR subunit
CREB	CAMP Response Element-binding Protein
CXCL12	C-X-C motif chemokine ligand 12
CX3CL1	C-X3-C motif chemokine ligand 1
DCC	Deleted in colorectal cancer
EMT	Epithelial-mesenchymal transition
Epac	Exchange protein activated by cAMP
ERK	Extracellular signal-regulated kinase
FAK	Focal adhesion kinase
FasL	Fas ligand
FMRP	Fragile X mental retardation protein
GABA	γ-Aminobutyric Acid
GAP-43	Growth-associated protein 43
GIST	Gastrointestinal stromal tumors
GKAP	Guanylate kinase associated protein
GSK-3β	Glycogen Synthase Kinase 3β
HSF1	Heat shock factor 1
ICC	intrahepatic cholangiocarcinoma
JNK	C-Jun N-terminal kinase
mAChRs	muscarinic cholinergic receptors
MAPK	Mitogen-Activated Protein Kinase
MDK	Midkine
mGluR1	Metabotropic glutamate receptor 1
MMP	Matrix metalloproteinase
nAChRs	nicotinic cholinergic receptors
NGF	Nerve Growth Factor
NK	Natural Killer
NMDAR	N-methyl-D-aspartate receptor
NPY	Neuropeptide Y
p75 NTR	P75 neurotrophin receptor
PDAC	pancreatic ductal adenocarcinoma
PD-L1	Programmed cell death 1 ligand 1
PI(5)P	Phosphatidylinositol 5-phosphate
PI3K	Phosphatidylinositol 3-kinase
PITPα	Phosphatidylinositol transfer protein-α
PNI	Perineural invasion
S4F	Semaphorin 4F

STAT3	Signal Transducer and Activator of Transcription 3
Synpo	Synaptic foot protein
TAMs	Tumor-Associated Macrophages
TAST	Tumor-Activated Schwann Cell Trajectories
TGFβ	Transforming growth factor beta
TIMP1	tissue inhibitor of matrix metalloproteinases 1
TM	Tumor microtubes
TME	tumor microenvironment
TNT	Tunneling nanotubes
Tregs	Regulatory T Cells
TrkB	Tropomyosin receptor kinase B
TrkC	Tropomyosin receptor kinase C
TRPV1	Transient receptor potential vanilloid type 1
Ttyh1	Tweety-homolog 1

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Authors' contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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