Molecular Cancer

REVIEW

Open Access

Hijacking of the nervous system in cancer: mechanism and therapeutic targets

Yu Zhang[1,2†], Qili Liao[1,2†], Xuyang Wen[1,2], Jiayan Fan[1,2], Tifei Yuan[3], Xuemei Tong[4], Renbing Jia[1,2*], Peiwei Chai[1,2*] and Xianqun Fan[1,2*]

Abstract

The activity of neurons in the vicinity of tumors is linked to a spectrum of cellular mechanisms, including the facilitation of tumor cell proliferation, synapse formation, angiogenesis, and macrophage polarization. This review consolidates the current understanding of neuro-oncological regulation, underscoring the nuanced interplay between neurological and oncological processes (termed as Cancer-Neuroscience). First, we elucidated how the nervous system accelerates tumor growth, metastasis, and the tumor microenvironment both directly and indirectly through the action of signaling molecules. Importantly, neural activity is also implicated in modulating the efficacy of therapeutic interventions, including immunotherapy. On the contrary, the nervous system potentially has a suppressive effect on tumorigenesis, further underscoring a dual-edged role of neurons in cancer progression. Consequently, targeting specific signaling molecules within neuro-oncological regulatory pathways could potentially suppress tumor development. Future research is poised to explore the intricate mechanisms governing neuro-tumor interactions more deeply, while concurrently refining treatment strategies for tumors by targeting the crosstalk between cancer and neurons.

Keywords Cancer, Nervous system, Neurotransmitters, Neurotrophic factors, Tumor microenvironment, Therapeutic implications

Introduction

The nervous system regulates the activities of various organs and systems, transmitting information that facilitates the body's response to environmental changes, thus maintaining homeostasis. Recent studies have identified a correlation between increased neural density within tumors and enhanced invasiveness [1–3]. Further research is gradually elucidating the distinct biological roles that nerves play in tumor dynamics [4, 5].

The investigation into the nervous system's regulation of tumors has evolved over time. In ancient Greek literature, tumors were termed "karkinos," a term that reflects early perceptions that did not systematically acknowledge the nervous system's significance in tumor biology. In 1889, Stephen Paget proposed the "seed and soil" hypothesis [6], which laid an early theoretical foundation for tumor microenvironment (TME) research. By the

†Yu Zhang and Qili Liao contributed equally to this work.

*Correspondence:
Renbing Jia
renbingjia@sjtu.edu.cn
Peiwei Chai
chaipeiwei123@sjtu.edu.cn
Xianqun Fan
fanxq@sjtu.edu.cn
[1] Department of Ophthalmology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200001, People's Republic of China
[2] Shanghai Key Laboratory of Orbital Diseases and Ocular Oncology, Shanghai 200001, People's Republic of China
[3] Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China
[4] Department of Biochemistry and Molecular Cell Biology, Shanghai Key Laboratory for Tumor Microenvironment and Inflammation, Key Laboratory of Cell Differentiation and Apoptosis of Chinese Ministry of Education, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

twentieth century, the tumor microenvironment theory had been formally established, shifting the understanding of tumor biology and recognizing the crucial role of the TME in tumor evolution [7]. Previously, nerves were thought to exist only in areas outside primary tumors, such as ganglia, leading to a greater emphasis on immune remodeling and angiogenesis within the TME[8, 9].

In this review, we synthesize current knowledge on neuro-oncological regulation, detailing how nerves influence tumor cells both directly and indirectly through the secretion of signaling molecules, including neurotransmitters and neurotrophic factors. These factors promote tumor proliferation [10] and metastasis [11], as well as enhance peripheral immune remodeling and increase angiogenesis [12] (Fig. 1). Although blocking neuroregulatory signals has been shown to inhibit tumor growth in various cancers, such as gliomas [13], prostate cancer [14], and ovarian cancer [15], the precise mechanisms by which nerves influence tumor progression remain inadequately understood. In addition, we have also observed that stimulating nerve activity in some tumors may exhibit anti-tumor effects, offering a broader perspective for neuro-oncological therapy. The purpose of this review is to integrate these

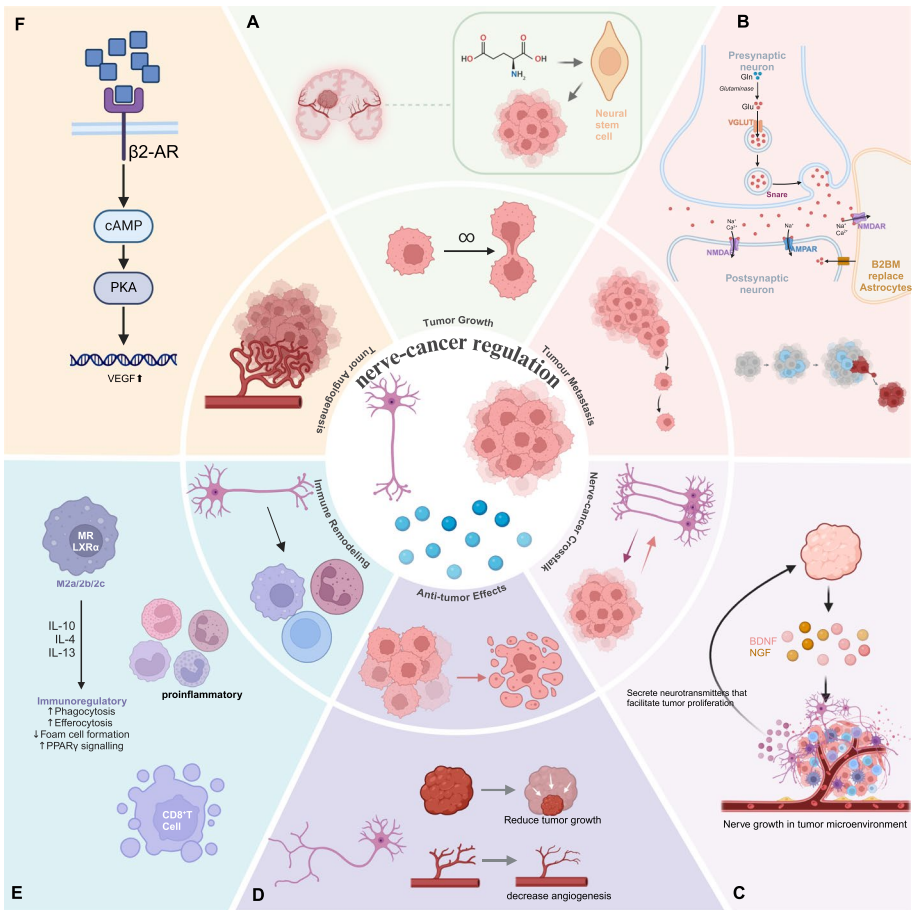

Fig. 1 Specific aspects of neuro-oncology regulation: **A** Neural activity regulates the differentiation direction of neural stem cells and promotes the proliferation of cancer cells by non-synaptically secreting neurotransmitters such as glutamate. **B** Neural activity can facilitate the metastasis of cancer cells. Breast cancer cells that have metastasized to the brain can replace astrocytes and surround normal nerve synapses, receive glutamate released from the presynaptic membrane, and activate the NMDAR signaling to promote the growth of tumors at the metastatic sites. **C** Interaction between nerves and tumors: Tumor cells can secrete signals such as BDNF and NGF to promote nerve growth into the microenvironment. Meanwhile, nerves can secrete neurotransmitters to promote tumor growth. **D** Anti-tumor effect of nerves: Nerves can inhibit tumors by reducing tumor growth and neovascularization. **E** Immunological remodeling of the tumor microenvironment by nerves: Nerves can regulate the differentiation of macrophages into the M2 type and have a pro-inflammatory effect. It increases the exhaustion of CD8 + T cells and creates an immunosuppressive microenvironment. **F** Nerves promote angiogenesis in the tumor microenvironment. Catecholamine stimulation can regulate vascular endothelial growth factor (VEGF) gene expression through β-adrenergic receptors. Original figure created with BioRender.com

findings and guide future research and treatment, adding new avenues for treating tumors.

Neuronal influence on cancer cell biology

Although it is well-established that nerves exert a regulatory effect on tumors—such as guiding tumor migration along neural pathway [16], the specific mechanisms through which nerves influence tumor cells in the interaction between the nervous system and tumor cells remain inadequately defined. Current research suggests that cancer cells may exhibit neuro-oncological addiction [17], with Fu Yan et al. providing important evidence for the neural regulation of cholangiocarcinoma [18]. Nerves not only promote the initiation and progression of tumors but also interact with them to create a positive feedback loop that continually facilitates tumor evolution. Furthermore, within the intricate interplay between nerves and tumors, nerves can also play an anti-tumor role under certain conditions [19].

Neuronal regulation of cancer growth and metastasis

The interaction between the nervous system and malignant tumors is highly complex. Current research indicates that in malignancies such as brain cancer, skin cancer, prostate cancer, and pancreatic cancer, neural activity can promote tumor cell proliferation and migration while also regulating their differentiation [20, 21]. In the context of tumors, cancer cells can secrete signaling molecules such as BDNF. BDNF binds to the tropomyosin receptor kinase B (TrkB) receptor, activating downstream MAPK signaling and transcription factors like FOS, which promote chromatin accessibility [22]. This facilitates neuronal differentiation and activates neurodevelopment-related signaling pathways [23]. Additionally, neuronal growth further secretes signaling molecules that promote tumor progression.

Gliomas, which arise from glial cells—supporting cells of the central nervous system—interact closely and complexly with both normal neural cells and other components of the nervous system, such as glial cells and blood vessels [24]. Consequently, gliomas, particularly glioblastomas, serve as a key model for studying how the nervous system contributes to tumor growth [25]. Thus, we focus on gliomas to illustrate the pro-tumorigenic effects of neural activity.

In glioblastoma (GBM), oligodendrocyte precursor cells (OPCs) are proposed as one of the cellular origins [26]. Neuronal activity influences tumor growth by secreting signaling molecules and disrupting OPCs homeostasis [27]. Specifically, non-synaptic release of neurotransmitters such as glutamate and γ-aminobutyric acid (GABA), maintaining neural stem cells and progenitor cells in a depolarized state, influencing tumor cell differentiation [28]. Neurons also secrete brain-derived neurotrophic factor (BDNF) via a paracrine mechanism, which binds to the TrkB receptor [29]. This interaction facilitates the trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPAR) to the glioma cell membrane, leading to an increased amplitude of glutamate-evoked currents within tumor cells. Enhanced depolarization current amplitude augments the plasticity of tumor synaptic strength, promoting glioma proliferation [30].

Additionally, the secretion of neuroligin-3 (NLGN3) from neurons and OPCs may act as a glioma mitogen regulated by neural activity, activating multiple oncogenic pathways within glioma cells [31]. This includes the phosphorylation of focal adhesion kinase (FAK) upstream of the PI3K-mTOR pathway, as well as classic FAK downstream signaling cascades involving SRC kinase, the PI3K-mTOR pathway, and the SHC-RAS-RAF-MEK-ERK pathway. The activation also encompasses increased phosphorylation of various integrins and growth factor receptors [32] (Fig. 2). Neuronal activity elicits a response in tumor cells, further stimulating the secretion of proteins such as NLGN3, establishing a positive feedback loop that perpetuates tumor proliferation.

The phenomenon of nerves promoting tumor growth extends beyond gliomas and has been observed in various other cancer types. In a mouse model of prostate cancer, the migration of DCX + neural progenitor cells was shown to enhance cancer cell growth [33]. In patients with head and neck squamous cell carcinoma and high-grade serous ovarian cancer, nerve formation was found to establish functional connections, which correlated with poor prognosis and tumor progression[34]. Additionally, in small cell lung cancer, sympathetic nerves activate protein kinase A signaling, thereby promoting cancer cell proliferation [35].

Nerves not only promote tumor proliferation but also act as physical conduits for cancer cell metastasis and facilitate vascular and lymphatic spread. Furthermore, nerves can enhance the invasive properties of tumor cells through interactions with them [36, 37]. In various malignant tumors, perineural invasion (PNI) is closely associated with metastasis, with tumor cells infiltrating neural tissues and propagating along nerves. In pancreatic cancer, cancer-associated fibroblasts (CAFs) amplify the interaction between tumor cells and nerves by releasing extracellular vesicles, which influence neural restructuring and promote PNI [38].

Studies have indicated that different types of neurons can regulate the development of various cancers. Specifically, in sensory neurons, an increase in intracellular calcium ions in dorsal root ganglia leads to the release of substance P (SP). This peptide activates the

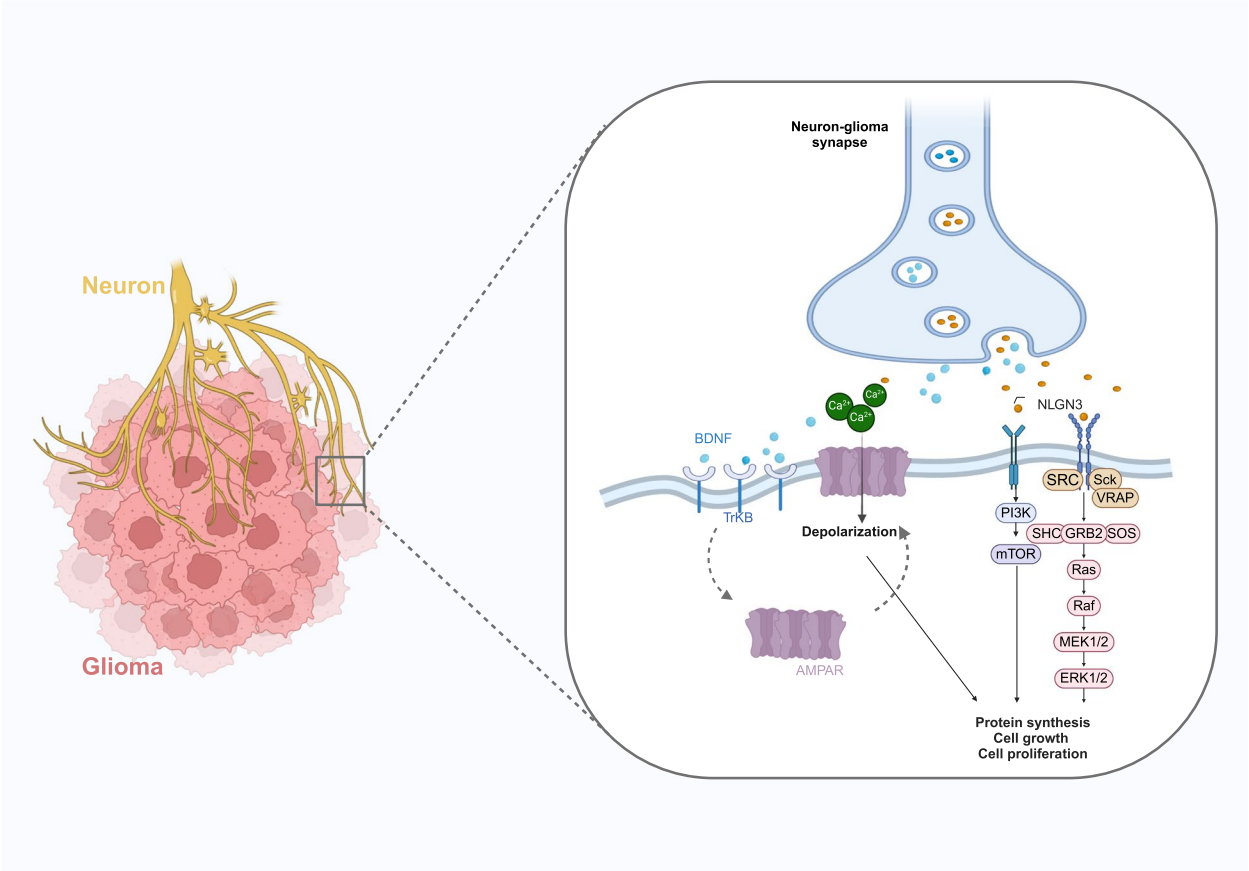

Fig. 2 Innervation in gliomas promotes tumor growth. Neurons secrete brain-derived neurotrophic factor (BDNF), which binds to TrKB receptor and promotes the transfer of AMPA receptor in tumor cytoplasm to cell membrane. The amplitude of glutamate-induced current increased, and the larger depolarization amplitude promoted the proliferation of glioma cells. Neuroligin −3 (NLGN3) secreted in an activity-dependent manner activates a variety of carcinogenic pathways in glioma cells, including the PI3K-mTOR cascade, SRC kinase cascade, and SHC-RAS-RAF-MEK-ERK cascade. Original figure created with BioRender.com

tachykinin receptor 1 (TACR1) on cancer cells, inducing apoptosis in some. The resulting dead cells release small single-stranded RNA (ssRNA), which activates Toll-like receptor 7 (TLR7) in neighboring cells, triggering the non-canonical phosphoinositide 3-kinase (PI3K) signaling pathway and promoting the invasion, proliferation, and metastasis of breast cancer cells [39].

In prostate cancer, both branches of the autonomic nervous system play complementary roles. Sympathetic nerve fibers are crucial in the early stages of cancer development through the activation of matrix β2 and β3 adrenergic receptors. On the other hand, mediate signals through Cholinergic receptor muscarinic 1 (CHRM1) in the matrix, primarily contributing to tumor cell invasion, migration, and distant metastasis [40].Furthermore, under castrate conditions, prostate cancer cells exhibit increased activation of CHRM1 and CHRM3 leading to enhanced resistance to treatment and promoting cancer cell growth and migration through the activation of FAK and Yes-associated protein (YAP) [38].

Interestingly, cancer cells can not only passively receive signals emitted by neurons but also actively adapt to neuronal mechanisms. By obtaining signals from synapses, cancer cells can promote their own metastasis. Zeng et al. discovered that breast-to-brain metastasis (B2BM) cells form pseudo-tripartite synapses with glutamatergic neurons. In this process, breast cancer brain metastasis cells surround the synaptic cleft, replacing the role of astrocytes in the normal cleft. and obtain glutamate released by presynaptic neurons to activate the N-methyl-D-aspartate receptor (NMDAR) pathway, thereby promoting breast cancer brain metastasis [41].

Similarly, Venkataramani et al. identified a specific cellular subset in GBM that exists in a transcriptionally in a neuron-like and neural progenitor cell-like state, These cells are not connected to other tumor cells or astrocytes but receive synaptic input from neurons. AMPAR

are enriched in these neuron-like, non-mesenchymal cells, allowing them to receive glutamate released from the presynaptic membrane. This glutamate reception increases tumor microtubule branching, turnover, and the average step length, significantly accelerating Levy-like movement. As a result, this cellular subset enhances its invasiveness by adapting to neuronal mechanisms [42].

Nerve-cancer crosstalk

In the field of neuro-oncology, it is widely believed that there is a significant interaction between tumors and nerves [43]. Not only do nerves regulate the progression of tumors, but tumor cells themselves also exhibit various neural and neurodevelopmental characteristics, allowing them to influence the structure and function of nerves [44]. For instance, Qu et al. discovered that tumor cells recruit glial cells into the tumor microenvironment, thereby promoting their own metastasis. In the case of small cell lung cancer (SCLC), SCLC cells secrete the brain development-related factor Reelin, attracting astrocytes to the brain metastasis tumor area. These astrocytes, in turn, promote the growth of SCLC cells by releasing factors that support neuronal survival [45].

Cancer cells within tumors often exhibit phenotypic heterogeneity, with the ability to regulate and reversibly switch between different states that confer distinct tumor-promoting capabilities [46]. This phenotypic plasticity allows tumor cells to adapt to the evolving TME and escape therapeutic interventions. Notably, Cancer cells share regulatory networks with embryonic nerve cells, and the use of epigenetic drugs that inhibit tumorigenesis (such as EZH2i, HDAC1i, HDAC3i, LSD1i, and DNMT1i) can induce neuronal-like differentiation of cancer cells[34]. In prostate cancer, basal cells are particularly enriched in genes associated with neurogenesis. These primary basal cells, when cultured in vitro can spontaneously or be induced to transform into nerve-like cells, thereby engaging in neural signal responses. This characteristic is associated with aggressive prostate cancer [47]. Moreover, there is growing evidence of synaptic communication between neurons and cancer cells. For instance, pseudo-tripartite synapses formed between breast cancer brain metastasis cells and neurons facilitate signal transmission. Similarly, malignant glioma cells can achieve synaptic electrical integration with neurons, enabling efficient signal exchange that may promote tumor growth and invasiveness [41].

In the central nervous system, signals secreted by brain tumors such as gliomas can induce abnormal synapse formation, enhance neuronal excitability, and contribute to the onset of epileptic seizures [48]. In the peripheral nervous system, tumor cells can induce axon genesis and invade nerve fibers, resulting in remodeling of peripheral neural circuits and the development of chronic pain syndromes [49]. Furthermore, neuronal activity has been shown to promote tumor proliferation in a circuit-specific manner. Tumors can also modulate neural activity by disrupting inhibitory interneurons, altering synaptogenesis [48].

Tumors driven by PIK3CA variants C420R and H1047R can exhibit selective network overexcitation and alterations in synaptic components during the early stages of tumorigenesis. These changes include an increase in excitatory synapses, a decrease in inhibitory synapses, and alterations in the synaptic gene cluster [50]. The bidirectional communication between neurons and tumor cells can form a positive feedback loop. Tumor cells release neurotrophic factors, such as Nerve growth factor (NGF) and BNDF, which attract nerve fibers to invade the tumor microenvironment. In turn, the neurotransmitters released by these nerve fibers stimulate the growth and metastasis of tumor cells [51].

In a low-glucose environment, cancer cells promote the production of calcitonin gene-related peptide (CGRP) by nociceptive nerves through the secretion of NGF. This neurogenic CGRP mediates the growth-promoting effect of nociceptive nerves on cancer cells [52]. Taking malignant glioma as an example, glutamate receptor genes and postsynaptic structural genes are widely expressed in tumor cells, and it has been shown that NLGN3 plays a role in glioma synapse formation, and some glioma cells exhibit long-term electrophysiological response to neuronal activity [53].

Anti-tumor effects of nerves

The nervous system's involvement in tumor development is intricate and multifaceted. It is not the case that all neural connections invariably stimulate the proliferation of all types of tumors. Rather, the nervous system impacts various tumors in distinct ways, both by directly affecting the tumor cells and by altering their surrounding microenvironment. Interestingly, in certain instances, neural activity has been observed to exert an anti-tumor effect, a phenomenon that has been documented in aggressive malignancies such as pancreatic and breast cancers. Activating sensory neurons can inhibit the development of melanoma, specifically manifested as reducing tumor growth and neovascularization, increasing tumor-infiltrating anti-tumor lymphocytes, and simultaneously reducing immunosuppressive cells [54].

In the progression of breast cancer, the parasympathetic nerve can enhance anti-tumor immunity by increasing the expression of interferon– γ (IFN – γ) on CD4 + and CD8 + tumor-infiltrating lymphocytes (TILs). It also reduces the level of pro-inflammatory factors,

alleviating local inflammatory infiltration, and inhibits M2 polarization of tumor-associated macrophages [55]. The parasympathetic nerve reflex circuit describes a mechanism in which stimulation of the parasympathetic nerve activates a specific subset of T cells that produce acetylcholine (Ach). These T cells regulate TNF-α production, thereby reducing inflammation[56]. Ach receptors are expressed on T cells, and muscarinic signaling also modulates T cell proliferation [57]. Cholinergic signaling, through the muscarinic receptor CHRM1, directly and indirectly suppresses the development of pancreatic cancer and the characteristics of cancer stem cells. In KC mice, subdiaphragmatic vagotomy accelerates the development of pancreatic cancer. Moreover, in both KC and KPC mice, knockout of the CHRM1 gene results in an increased area of pancreatic intraepithelial neoplasia, higher tumor incidence, and shortened survival [58].

Furthermore, in an enriched environment, elevated levels of norepinephrine (NE) and epinephrine (EPI) in mouse serum enhance β-adrenergic receptor (β-AR) signaling, both in tumor cells and in tumor-infiltrating myeloid cells. Activation of β-AR signaling plays a crucial role in reshaping the tumor microenvironment, directing it toward a state that promotes anti-tumor immunity, thereby inhibiting tumor growth [59].

Moreover, the nervous system plays a critical role in regulating the secretion of cytokines and peptides, which are pivotal in cancer progression. For instance, selective resection of splenic nerves has been shown to accelerate tumorigenesis in the Azoxymethane (AOM)/Dextran Sodium Sulfate (DSS) model [60]. splenic trefoil factor family 2, an anti-inflammatory peptide released by memory T cells under the influence of the vagus nerve, inhibits the expansion of myeloid-derived suppressor cells (MDSCs) through chemokine receptor 4 (CXCR4), thus contributing to the anti-inflammatory reflex arc.

The nervous system regulates tumor behavior through various signaling molecules, such as neuronal activity or neurotransmitter secretion, which can either stimulate tumorigenesis, proliferation, and migration or exert an inhibitory effect on growth in certain tumors. This highlights the importance of developing more specific therapeutic strategies, with an emphasis on precision medicine, in future tumor treatments.

Nervous system and tumor microenvironment

The nervous system can both directly influence tumor cells and indirectly modulate their development by regulating other cellular components within the TME [52]. The TME encompasses the milieu surrounding tumor cells and exerts a significant impact on tumorigenesis, metastasis, and the tumor's response to therapeutic interventions [61]. Historically, TME has been characterized by the presence of tumor cells, a spectrum of immune cell types, stromal cells, vascular cells, extracellular matrix, and an array of signaling molecules. However, recent insights suggest that the nervous system also plays a pivotal role in this highly heterogeneous and dynamic milieu [62–64].

The nervous system alters the TME through the secretion of signaling molecules and further influences tumor cell biological behavior by promoting immune suppression, immune remodeling [65], and angiogenesis within the microenvironment [66]. In a reciprocal manner, cancer cells can secrete neurotrophic factors and exosomes, which in turn can induce neurogenesis within the TME [67]. Collectively, these bidirectional interactions establish a complex regulatory network, where both the nervous system and tumor cells actively shape each other's behavior, contributing to the dynamic and evolving nature of the TME.

Neuroimmune crosstalk in cancer

The balance of the immune system is crucial to human health. As it plays a vital role in recognizing and eliminating foreign pathogens, as well as monitoring and clearing abnormal cells within the body, such as cancer cells [68]. In contrast, the nervous system is responsible for receiving, processing, integrating, and transmitting information, thus regulating various physiological activities [69]. Although traditionally regarded as separate entities, both neurons and glial cells in the nervous system can modulate immune cells within the TME [70], thereby shaping the immune landscape and impacting therapeutic efficacy [71–73].

The activation of the sympathetic nervous system (SNS) can influence the tumor microenvironment through direct neural innervation, hormonal regulation, and indirect modulation [74]. This activation suppresses immune responses, induces cell apoptosis, and facilitates cancer cell metastasis, thereby impacting both immune responses and cancer cell behavior through multiple mechanisms [75].

Direct neural innervation refers to the direct entry of SNS nerve fibers into tumor tissue, releasing neurotransmitters [74]. Neurotransmitters released by nerve fibers, such as NE, dopamine, acetylcholine, etc., can directly act on corresponding receptors on tumor cells and immune cells, thereby regulating immune responses. For example, β-adrenergic signaling can inhibit T cells from secreting interferon-γ, affecting cellular immune function [51]. Hormonal regulation refers to the arrival of adrenaline at tumor tissue through blood circulation [74]. Activation of β2-ARs leads to STAT3 phosphorylation in MDSCs, increasing their resistance to Fas/FasL-induced apoptosis and significantly promoting their proliferation and

suppressive function [76]. Indirect modulation refers to the SNS's regulation of the physiological functions of distant tissues, indirectly affecting the tumor microenvironment [74]. For instance, SNS modulates the bone marrow microenvironment and regulates immune cell production, thereby promoting tumor cell metastasis [77, 78]. The vagus nerve can affect tumor proliferation by inhibiting the SNS or indirectly inducing β-adrenergic signaling, and its role in cancer varies depending on the type of cancer [79].

Neurotransmitters and neuropeptides released by other nerves also play an important regulatory role in the nervous system. Since the majority of research on the effects of neurosignaling molecules on tumors is conducted in vitro or using animal models, Hou et al. suggest that neuroendocrine tumors provide an appropriate human model for investigating the role of neurotransmitters. In medullary thyroid carcinoma, CGRP shapes an immunosuppressive microenvironment[80]. Neuropeptides released by nociceptive receptors, such as CGRP and SP, have regulatory effects on immune and inflammatory responses. CGRP can suppress inflammation by regulating macrophage polarization and cytokine expression, and it can also directly promote the exhaustion of cytotoxic $CD8^+$ T cells, limiting their ability to clear melanoma [81]. SP, on the other hand, promotes T lymphocyte survival and the secretion of pro-inflammatory cytokines.

Tumor-associated nerves express immune checkpoint molecules in the tumor microenvironment, such as PD1 and PDL-1, leading to T cell suppression and promoting cancer progression. Nerves dynamically regulate the effectiveness of immunotherapy by modulating the metabolism of the TME. NGF promotes nerve infiltration into the TME. In pancreatic cancer, Li et al. demonstrated that nerve infiltration releases glutamate, which enhances glycolysis in tumor cells [82]. Similarly, the neurotransmitter 5-HT activates the PI3K/Akt/mTOR signaling pathway, driving metabolic reprogramming and significantly promoting glycolysis in non-small cell lung cancer. This metabolic reprogramming exacerbates immune suppression within the TME. Notably, neutralizing 5-HT-mediated tumor immune metabolic reprogramming in mice improves the efficacy of PD-1 monoclonal antibody therapy [83].

Neural signaling in tumor angiogenesis

The vascular system supplies essential oxygen and nutrients to neuronal cells while aiding in the clearance of metabolic waste. Neuronal activity governs the constriction or dilation of blood vessels. Anatomically, nerves and blood vessels often run in parallel[84], forming neurovascular bundles to meet each other's mutual demands. In the tumor microenvironment, neuro-derived signals activate signaling pathways that promote the production of pro-angiogenic factors within the tumor microenvironment [85].

Neuronal axons can guide the differentiation and patterning of arteries, and smooth muscle cells surrounding arteries release factors that can also guide neuronal growth[86]. Sympathetic nerve terminals release NE to stimulate the ADRβ2 receptors on endothelial cells, inhibit oxidative phosphorylation, and promote aerobic glycolysis, upon which endothelial cells rely for angiogenesis [51]. In prostate cancer, the absence of ADRB2 leads to enhanced oxidative phosphorylation in endothelial cells, increased glucose uptake, and changes in mitochondrial gene expression, such as increased expression of CoA6. In in vivo experiments, co-transplantation of CoA6-overexpressing endothelial cells with PC-3 prostate cancer cells significantly inhibits angiogenesis and tumor growth[87]. Under chronic stress, ADRB2 can regulate vascular endothelial growth factor (VEGF) expression through the cAMP-PKA signaling pathway, and stress-induced VEGF protein and mRNA are significantly elevated within tumor tissues [88].

Sympathetic nerves can also indirectly affect tumor angiogenesis by modulating the activity of immune cells. For instance, macrophage infiltration in the tumor microenvironment can be activated by sympathetic signals to release various angiogenic factors, including VEGF, and provide channels for endothelial cell migration [51]. Neurotransmitters, NGF [89], BDNF, angiogenin, fibroblast growth factor, tumor necrosis factor-alpha, and transforming growth factor-beta are among the signaling molecules that can regulate tumor angiogenesis [90]. The BDNF/TrkB system is crucial for tumor angiogenesis and growth and may serve as a potential target for anti-angiogenic therapy in Hepatocellular carcinoma [91, 92]. The intricate interplay between nerves and blood vessels forms a complex network, highlighting the therapeutic potential of targeting neuro-mediated pathways as an innovative strategy for regulating tumor angiogenesis and, consequently, tumor proliferation.

Therapeutic implications

In the 1960s, vagotomy was first used to treat benign gastric ulcers, and later this technique was applied to the treatment of early gastric cancer. Vagotomy suppresses the Wnt signaling pathway in gastric cancer, reduces the amplification of stem cells, and significantly decreases the incidence and progression of gastric cancer. However, due to the limitations of gastric cancer metastasis models, the impact of nerve dissection on other organs is not yet determinable[93]. As our understanding of the role of nerves in regulating tumor behavior within the

tumor microenvironment deepens, the means of treating tumors are also continuously evolving. Nerves can affect cancer cells in two ways: one is by directly affecting the biological activities of tumor cells [41], and the other is indirectly by affecting other cells within the tumor microenvironment [80]. Moreover, some cancer cells can utilize nerves to obtain nutrients, and certain nerve signals can directly induce anti-apoptotic changes in cancer cells [74]. Therefore, developing targeted therapeutic strategies that can block the neuro-tumor regulatory process, targeting the neurotransmitters and signaling pathways involved in these regulatory processes, seems very promising[94, 95] (Fig. 3). Numerous clinical trials are currently underway targeting the blockade of these pathways (Table 1).

Inhibit nerve action on tumor cells

The expression of glutamate receptors and genes related to postsynaptic structures are widely present in cancer cells, and neural activity secretes signals, which stimulate tumor progression. Therefore, targeting the direct interaction between nerves and tumors is also a promising direction for development. In the previously mentioned pseudo-tripartite synapse formation in brain metastatic breast cancer, mice with knocked-down NMDAR GluN2B subunits exhibited significantly longer survival without brain metastasis and lower brain metastasis burden compared to non-knockdown mice, which is supported by relevant data from the TCGA database [41].

NGF serves as a key signaling molecule in the positive feedback loop of neuro-oncological regulation. Thus, blocking neurotrophic factors or their receptors could represent a new therapeutic direction [96]. Cholinergic stimulation of gastric epithelium induces the expression of NGF, and in turn, the overexpression of NGF within gastric epithelium expands intestinal nerves and promotes carcinogenesis. Hayakawa et al. found that blocking NGF/Trk signaling in an CHRM3-dependent manner inhibits epithelial cell proliferation and tumorigenesis [97]. Meanwhile, Zhang et al. also pointed out that targeting NGF to block neurogenesis provides a new direction for many cancers, such as pancreatic cancer[98].

TrkB is the primary receptor for BDNF, and in nude mice, co-expression of TrkB/BDNF can cause tumor

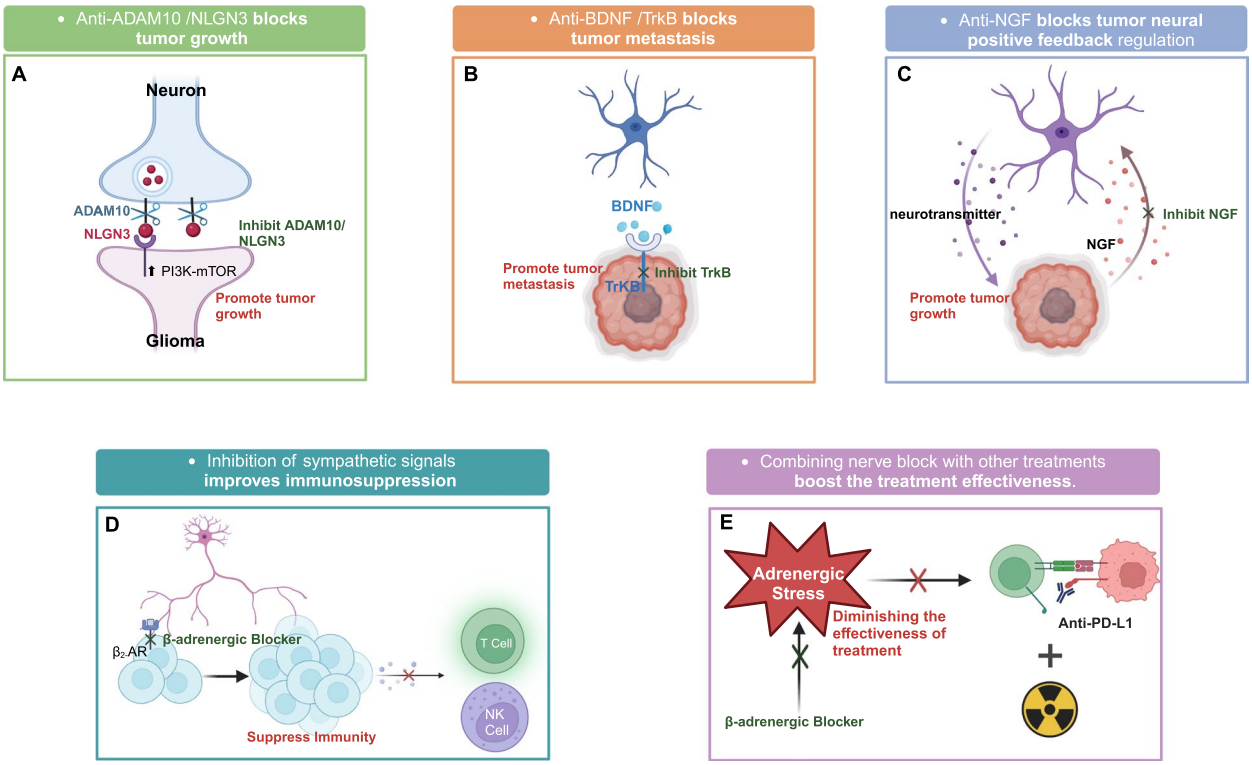

Fig. 3 Several example mechanisms of therapeutic avenues of cancer neuroscience: **A** Inhibit of ADAM10/NLGN3 can suppress glioma growth by targeting its downstream PI3K-mTOR signaling pathway. **B** Neurosecretion-derived BDNF promotes tumor metastasis by binding to the TrkB receptor. Inhibition of BDNF-TrkB binding can suppress tumor metastasis. **C** Blocking the NGF-mediated neuro-tumor positive feedback loop. **D** Inhibiting sympathetic nerve signaling can mitigate the immunosuppressive microenvironment of the tumor. **E** The combination of β-blockers and immunosuppressants can augment the anti-tumor efficacy of anti-PD-L1 therapy. NLGN3 = Neuroligin-3. BDNF = brain derived neurotrophic factor. NGF = nerve growth factor. Original figure created with BioRender.com

Table 1 Clinical trials targeting the tumor–nerve axis

Cancer	Therapy	Target	Phase	Primary Outcome Measures	Status	Outcome	Reference
Primary Colon and Rectal Cancer	Propranolol and Etodolac	β-adrenergic Blocker and COX-2 Inhibitor	Phase 2	5-year disease-free-survival	ongoing	Reduce systemic inflammation and the biomarkers related to tumor metastasis	NCT03919461
colorectal cancer	Propranolol and Etodolac	β-adrenergic Blocker and COX-2 Inhibitor	Phase 3	3-year reccurence and metastasis	completed	No significant difference	NCT00888797
Pancreatic Cancer	Propranolol and Etodolac	β-adrenergic Blocker and COX-2 Inhibitor	Phase 2	Rate of cancer recurrence	ongoing	Reduced metastatic potential	NCT03838029
Spinal Hemangioma	Atenolol and Propranolol	β-adrenergic Blocker	Phase 4	3-month and 6-month reducing tumor growth	ongoing	Not reported	NCT05106179
Prostate cancer	Carvedilol	β-adrenergic Blocker	Phase 2	The change of the biomarkers	ongoing	Nerve infiltration is associated with a poorer prognosis	NCT02944201
Melanoma	Pembrolizumab and Propranolol Hydrochloride	β-adrenergic Blocker	Phase 1 Phase 2	Effective rate of immune-related response	ongoing	Not reported	NCT03384836
Multiple Myeloma	Propranolol	β-adrenergic Blocker	Not Applicable	Changes in immune cell subsets	ongoing	Not reported	NCT05312255
Breast Cancer	Propranolol and chemotherapy	β-adrenergic Blocker	Phase 2	Compliance	completed	The compliance and target measurement of propranolol were obtained	NCT01847001
Schwannomatosis	Tanezumab	Antibody against NGF	Phase 3	Change in pain	ongoing	not reported	NCT03992170
Glioma	Perampanel	AMPAR inhibitor	Phase 4	Proportion of patients with seizures reduced by 50% or more	completed	No data displayed	NCT02363933
High Grade Glioma	Perampanel	AMPAR inhibitor	Phase 1 Phase 2	Peritumoral HFO Rate	completed	No significant remission of peritumoral hyperexcitability	NCT04497142
Prostate cancer	Amantadine	NMDAR antagonist	Phase 1 Phase 2	The degree of pain relief	Unknown	Not reported	NCT00188383
Glioblastoma	Combination Drug Therapy	combination drugs Including NMDAR inhibitor	Phase 1	1-year tumor remission	completed	Not reported	NCT02654964
Glioblastoma	ONC201	DRD2/3 inhibitor	Phase 2	Objective response rate	ongoing	Not reported	NCT04629209
Glioma	ONC201	DRD2/3 inhibitor	Phase 2	Overall response rate	ongoing	Not reported	NCT03295396
Recurrent Diffuse Midline Gliomas	ONC206	DRD2 inhibitor	Phase 1	Dose-limiting toxicity	ongoing	Not reported	NCT04732065
Gliomas	ONC201	DRD2/3 inhibitor	Phase 1	Determination of recommended Phase 2 dose	ongoing	Not reported	NCT03416530

COX-2 cyclooxygenase 2, *NGF* nerve growth factor, *DRD2* dopamine receptor D2, *DRD3* dopamine receptor D3, *NLGN3* Neuroligin-3, *AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors, *NMDAR* N-methyl-D-aspartate receptor

systemic metastasis by inhibiting the physiological barrier to metastasis, anoikis, and activating the PI3K/PKB signaling pathway. Therefore, we speculate that TrkB-targeted therapy may have therapeutic potential for human tumors that overexpress or have mutations in TrkB [99].

NLGN3 is a key protein involved in the formation of synapses in gliomas. In this process, it is secreted from neurons and oligodendrocyte precursor cells [32]. ADAM10, as a key enzyme, is involved in the secretion process of NLGN3, making targeting ADAM10 or NLGN3 a new therapeutic direction. ADAM10 inhibitors, such as INCB7839, can inhibit the secretion of NLGN3 from tumor cells, thereby blocking the signal transmission between neurons and tumor cells and effectively preventing the growth of high-grade gliomas xenografts. Pan et al. found that in optic gliomas, mutations in NF1 in retinal neurons lead to an abnormal increase in NLGN3 shedding in the optic nerve and correspondingly increased retinal neuron activity. Genetic NLGN3 deficiency or pharmacological inhibition of NLGN3 shedding can prevent the formation and progression of NF1-OPG [100].

Dopamine and dopamine receptor 2 (DRD2), are overexpressed in clinical GBM specimens. DRD can promote cell proliferation through the GNAI2/Rap1/Ras/ERK signaling axis, and its antagonists can inhibit tumor cell growth [101]. Cancer neuroscientists have enhanced our understanding of the mechanisms of tumor-neuron-glial interactions, making molecular targeted strategies promising for clinical impact. In the future, new materials and other means can be used to target the modulation of neuro-oncological interactions to alleviate cancer recurrence and progression [94, 102].

Targeted regulation of the tumor microenvironment

The tumor microenvironment plays a role analogous to soil in tumor dissemination [103], and the nervous system regulates it by stimulating endothelial cells, immune cells, and so on. Studies have shown that mental stress and stress can promote tumor growth [104, 105]. Sarkar et al. found that reducing systemic stress through transplantation of neurons producing beta-endorphin can activate innate immunity, regulate the ratio of pro-inflammatory to anti-inflammatory cytokines, thereby inhibiting the development of cancer [106].

Drugs targeting neurotransmitters and their receptors also show potential clinical significance in cancer treatment [107]. For instance, Zhao et al. discovered that using atenolol to block adrenergic beta receptors can prevent T-cell exhaustion, enhance T-cell function, and when used in combination with immune checkpoint blockade, it provides a new strategy for cancer immunotherapy[108]. In the treatment of anti-PD-L1 checkpoint immunotherapy combined with radiotherapy, adrenergic stress interferes with the therapeutic effect, and the use of beta-blockers can overcome this interference [109].

Concurrently, Chang et al. also found that when using anthracycline chemotherapy drugs, these drugs increase sympathetic nerve signal activity, affecting the tumor microenvironment, and thus the use of beta-receptor blockers can enhance the therapeutic effect of chemotherapy drugs [110]. Currently, many clinical trials of beta-receptor antagonists combined with other therapies for the treatment of cancer are underway (Table 1). In addition to beta-receptors, the receptor for another neurotransmitter, 5-hydroxytryptamine (5-HT), 5-hydroxytryptamine receptor 2B (HTR2B), is significantly upregulated in human gastric adenocarcinoma tissue. In a subcutaneous xenograft model, both HTR2B gene silencing and treatment with the HTR2B antagonist SB204741 can significantly reduce gastric tumor burden [111].

Furthermore, tumors can also regulate their own survival environment by affecting nerves. Under hypoxic conditions, gliomas produce high levels of glutamate to stimulate local neuronal activity, and neuronal secretion of exosomes promotes the M2 polarization of microglia. The use of the anti-epileptic drug levetiracetam can block the activation of neurons in GBM, inhibiting tumor progression [112]. These findings further confirm the role of the nervous system in tumor development and the potential importance of neurotransmitters and their receptors in cancer treatment.

Conclusion remarks and future directions

Neuro-oncology introduces a novel regulatory paradigm where the nervous system, while sensing the physiological state of the body, also participates in the progression of diseases under pathological conditions such as cancer. Neural activity can influence the behavior of immune cells, promote vascular formation, and enhance glycolysis within the TME, all of which provide a more conducive environment for tumor survival.

Furthermore, cancer cells themselves promote their spread by affecting neurogenesis. The discoveries in this emerging field have not only made us aware of the regulatory role of the nervous system on tumors but also led us to consider that we might be able to use the tumor's regulatory effects on the nervous system to further understand activities such as neural plasticity. Consequently, various drugs targeting the neuro-oncological interaction pathways are currently being developed for cancer treatment, and the reshaping of the tumor microenvironment by the nervous system can be combined with immunotherapy.

Numerous therapeutic strategies are currently undergoing clinical trials, marking a significant advancement in cancer treatment. However, the field of neuro-oncological regulation still faces certain challenges. One major limitation is the unintended disruption of normal neural signaling caused by drugs designed to inhibit neural secretion. The inhibitors of neural signaling result in neurological disorders, including peripheral sensory abnormalities and focal mononeuropathy induced by anti-NGF antibodies. Additionally, joint-related adverse events may occur[113]. BDNF and its receptor, TrkB, play a crucial role in alleviating anxiety and depression; inhibition of BDNF can trigger mood disorders. This underscores the need for more precise and sophisticated approaches to selectively modulate the nervous system's involvement in tumor biology while preserving the integrity of healthy neural functions [114]. Additionally, since tumors can promote neurogenesis and increase the excitability of the nervous system, they can also lead to neurological disorders such as epilepsy [48]. How to control the condition through neural regulatory means is also a question we should consider. Given the important role of neural signals in various cellular processes, it is crucial to thoroughly investigate the potential mechanisms underlying changes in tumor behavior mediated by neural activity in future research work. Current nanoparticle-based drug delivery systems enhance drug stability and targeting efficiency, with the potential to overcome biological barriers, including the blood–brain barrier [115]. Perhaps in the future, we can use new-generation materials to more precisely deliver drugs to the tumor microenvironment and control the range of action [114].

Considering the complex and diverse interactions between nerves and tumors, it is necessary to further understand the detailed roles of different nerves in various tumors and establish more accurate models. This will not only deepen our theoretical understanding but also offer valuable insights for improving the treatment of tumors and addressing neurological disorders in the future.

Abbreviations

TME	Tumor microenvironment
BDNF	Brain-derived neurotrophic factor
TrkB	Tropomyosin receptor kinase B
OPCs	Oligodendrocyte precursor cells
GABA	Glutamate and γ-aminobutyric acid
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors.
NLGN3	Neuroligin-3
FAK	Focal adhesion kinase
CAFs	Cancer-associated fibroblasts
PNI	Perineural invasion
SP	Substance P
TACR1	Tachykinin receptor 1
ssRNA	Single-stranded RNA
TLR7	Toll-like receptor 7
CHRM	Cholinergic receptor muscarinic 1
YAP	Yes1-associated protein
B2BM	Breast-to-brain metastasis
NMDAR	N-methyl-D-aspartate receptor
GBM	Glioblastoma
SCLC	Small cell lung cancer
NGF	Nerve growth factor
CGRP	Calcitonin gene-related peptide
IFN – γ	Interferon– γ
TILs	Tumor-infiltrating lymphocytes
Ach	Acetylcholine
MDSCs	Myeloid-derived suppressor cells
CXCR-4	Chemokine receptor 4
AOM	Azoxymethane
DSS	Dextran Sodium Sulfate
NE	Norepinephrine
EPI	Epinephrine
β-AR	β-Adrenergic receptor
SNS	Sympathetic nervous system
VEGF	Vascular endothelial growth factor
DRD2	Dopamine receptor D2
5-HT	5-Hydroxytryptamine
HTR2B	5-Hydroxytryptamine receptor 2B

Acknowledgements
Not applicable.

Authors' contributions
Y Z., Q.L.L., R.B.J., P.W.C. and X.Q.F wrote and revised abstract. Y. Z. and Q.L.L wrote and revised neuronal influence on cancer cell biology. Y Z., X.Y.W., J.Y.F., X.M.T and T.F.Y wrote and revised nervous system and tumor microenvironment. Y Z., Q.L.L, X.Y.W., J.Y.F. X.M.T and T.F.Y wrote and revised therapeutic implications. P.W.C critically revised the manuscript; Y Z., Q.L.L., R.B.J., P.W.C. and X.Q.F designed the structure of the review article, supervised the analysis and drafted the manuscript. All authors reviewed final manuscript.

Funding
Funding for open access charge: National Natural Science Foundation of China [82373298, 82388101, U23A20466]; Science and Technology Commission of Shanghai [20DZ2270800, 23ZR1438400, 23ZR1480100, 23YF1422400]; China Postdoctoral Science Foundation [2023M732290]; Shanghai Key Clinical Specialty, Shanghai Eye Disease Research Center [2022ZZ01003]; Innovative Research Team of High-level Local Universities in Shanghai [SHSMU-ZDCX20210900, SHSMU-ZDCX20210902]; Shanghai Municipal Health Commission (GWVI-11.2-YQ19).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 5 January 2025 Accepted: 22 January 2025
Published online: 06 February 2025

References

1. Reavis HD, Chen HI, Drapkin R. Tumor Innervation: Cancer Has Some Nerve. Trends Cancer. 2020;6:1059–67.
2. Ayala G. Neuroepithelial Interactions in Cancer. Annu Rev Pathol. 2023;18:493–514.

3. Zhu Y, Yao L, Gallo-Ferraz AL, Bombassaro B, Simoes MR, Abe I, Chen J, Sarker G, Ciccarelli A, Zhou L, et al. Sympathetic neuropeptide Y protects from obesity by sustaining thermogenic fat. Nature. 2024;634:243–50.
4. Gregory E, Dugan R, David G, Song YH. The biology and engineered modeling strategies of cancer-nerve crosstalk. Biochim Biophys Acta Rev Cancer. 2020;1874: 188406.
5. Hondermarck H, Jiang CC. Time to Introduce Nerve Density in Cancer Histopathologic Assessment. Clin Cancer Res. 2023;29:2342–4.
6. Paget S. The distribution of secondary growths in cancer of the breast. 1889. Cancer Metastasis Rev. 1989; 8:98–101.
7. Ogata M, Shimizu J, Kosaka H, Maekawa R, Shimizu K, Fujiwara H, Hamaoka T. Expression of H-2 antigens and inducibility of antitumor immune responses in various tumor cell clones established from methylcholanthrene-induced fibrosarcomas. Jpn J Cancer Res. 1986;77:1134–41.
8. Amit M, Anastasaki C, Dantzer R, Demir IE, Deneen B, Dixon KO, Egeblad M, Gibson EM, Hervey-Jumper SL, Hondermarck H, et al. Next Directions in the Neuroscience of Cancers Arising outside the CNS. Cancer Discov. 2024;14:669–73.
9. Jung E, Alfonso J, Monyer H, Wick W, Winkler F. Neuronal signatures in cancer. Int J Cancer. 2020;147:3281–91.
10. Kobayashi H, Iida T, Ochiai Y, Malagola E, Zhi X, White RA, Qian J, Wu F, Waterbury QT, Tu R, et al. Neuro-Mesenchymal Interaction Mediated by a beta2-Adrenergic Nerve Growth Factor Feedforward Loop Promotes Colorectal Cancer Progression. Cancer Discov. 2025;15:202–26.
11. Kuol N, Stojanovska L, Apostolopoulos V, Nurgali K. Role of the nervous system in cancer metastasis. J Exp Clin Cancer Res. 2018;37:5.
12. Zhou S, Li J, Yu J, Wang Y, Wang Z, He Z, Ouyang D, Liu H, Wang Y. Tumor microenvironment adrenergic nerves blockade liposomes for cancer therapy. J Control Release. 2022;351:656–66.
13. Lehrman EK, Stevens B. Shedding light on glioma growth. Cell. 2015;161:704–6.
14. Chen WY, Wen YC, Lin SR, Yeh HL, Jiang KC, Chen WH, Lin YS, Zhang Q, Liew PL, Hsiao M, et al. Nerve growth factor interacts with CHRM4 and promotes neuroendocrine differentiation of prostate cancer and castration resistance. Commun Biol. 2021;4:22.
15. Bayraktar E, Chen S, Corvigno S, Liu J, Sood AK. Ovarian cancer metastasis: Looking beyond the surface. Cancer Cell. 2024;42:1631–6.
16. Li J, Kang R, Tang D. Cellular and molecular mechanisms of perineural invasion of pancreatic ductal adenocarcinoma. Cancer Commun (Lond). 2021;41:642–60.
17. Magnon C, Hondermarck H. The neural addiction of cancer. Nat Rev Cancer. 2023;23:317–34.
18. Fu Y, Shen K, Wang H, Wang S, Wang X, Zhu L, Zheng Y, Zou T, Ci H, Dong Q, Qin LX. Alpha5 nicotine acetylcholine receptor subunit promotes intrahepatic cholangiocarcinoma metastasis. Signal Transduct Target Ther. 2024;9:63.
19. Pan S, Yin K, Tang Z, Wang S, Chen Z, Wang Y, Zhu H, Han Y, Liu M, Jiang M, et al. Stimulation of hypothalamic oxytocin neurons suppresses colorectal cancer progression in mice. Elife. 2021;10:e67535.
20. Venkatesh H, Monje M. Neuronal Activity in Ontogeny and Oncology. Trends Cancer. 2017;3:89–112.
21. Ouyang S, Shi S, Ding W, Ge Y, Su Y, Mo J, Peng K, Zhang Q, Liu G, Xiao W, et al. Neuropeptide Precursor VGF Promotes Liver Metastatic Colonization of Galphaq Mutant Uveal Melanoma by Facilitating Tumor Microenvironment via Paracrine Loops. Adv Sci (Weinh). 2024;11: e2407967.
22. Ibarra IL, Ratnu VS, Gordillo L, Hwang IY, Mariani L, Weinand K, Hammaren HM, Heck J, Bulyk ML, Savitski MM, et al. Comparative chromatin accessibility upon BDNF stimulation delineates neuronal regulatory elements. Mol Syst Biol. 2022;18: e10473.
23. Boilly B, Faulkner S, Jobling P, Hondermarck H. Nerve Dependence: From Regeneration to Cancer. Cancer Cell. 2017;31:342–54.
24. Weller M, Wen PY, Chang SM, Dirven L, Lim M, Monje M, Reifenberger G. Glioma Nat Rev Dis Primers. 2024;10:33.
25. Salvalaggio A, Pini L, Bertoldo A, Corbetta M. Glioblastoma and brain connectivity: the need for a paradigm shift. Lancet Neurol. 2024;23:740–8.
26. Xiong A, Zhang J, Chen Y, Zhang Y, Yang F. Integrated single-cell transcriptomic analyses reveal that GPNMB-high macrophages promote PN-MES transition and impede T cell activation in GBM. EBioMedicine. 2022;83: 104239.
27. Taylor KR, Monje M. Neuron-oligodendroglial interactions in health and malignant disease. Nat Rev Neurosci. 2023;24:733–46.
28. Keough MB, Monje M. Neural Signaling in Cancer. Annu Rev Neurosci. 2022;45:199–221.
29. Wang CS, Kavalali ET, Monteggia LM. BDNF signaling in context: From synaptic regulation to psychiatric disorders. Cell. 2022;185:62–76.
30. Taylor KR, Barron T, Hui A, Spitzer A, Yalcin B, Ivec AE, Geraghty AC, Hartmann GG, Arzt M, Gillespie SM, et al. Glioma synapses recruit mechanisms of adaptive plasticity. Nature. 2023;623:366–74.
31. Venkatesh HS, Johung TB, Caretti V, Noll A, Tang Y, Nagaraja S, Gibson EM, Mount CW, Polepalli J, Mitra SS, et al. Neuronal Activity Promotes Glioma Growth through Neuroligin-3 Secretion. Cell. 2015;161:803–16.
32. Venkatesh HS, Tam LT, Woo PJ, Lennon J, Nagaraja S, Gillespie SM, Ni J, Duveau DY, Morris PJ, Zhao JJ, et al. Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma. Nature. 2017;549:533–7.
33. Mauffrey P, Tchitchek N, Barroca V, Bemelmans AP, Firlej V, Allory Y, Romeo PH, Magnon C. Progenitors from the central nervous system drive neurogenesis in cancer. Nature. 2019;569:672–8.
34. Restaino AC, Walz A, Vermeer SJ, Barr J, Kovacs A, Fettig RR, Vermeer DW, Reavis H, Williamson CS, Lucido CT, et al. Functional neuronal circuits promote disease progression in cancer. Sci Adv. 2023;9:eade4443.
35. Fnu T, Shi P, Zhang W, Chung SSW, Damoci CB, Fang Y, Chen QY, Saqi A, Huang Y, Wu X, et al. Sympathetic neurons promote small cell lung cancer through the beta-2 adrenergic receptor. Cancer Discov. 2024. https://doi.org/10.1158/2159-8290.CD-24-0718.
36. Shi DD, Guo JA, Hoffman HI, Su J, Mino-Kenudson M, Barth JL, Schenkel JM, Loeffler JS, Shih HA, Hong TS, et al. Therapeutic avenues for cancer neuroscience: translational frontiers and clinical opportunities. Lancet Oncol. 2022;23:e62–74.
37. Gao X, Wang Q, Huang T, Xu C, Yang X, Zhang L, Wang J, Yang L, Zheng X, Fan Q, et al. Cervical cancer-produced neuromedin-B reprograms Schwann cells to initiate perineural invasion. Cell Death Dis. 2024;15:636.
38. Goto Y, Ando T, Izumi H, Feng X, Arang N, Gilardi M, Wang Z, Ando K, Gutkind JS. Muscarinic receptors promote castration-resistant growth of prostate cancer through a FAK-YAP signaling axis. Oncogene. 2020;39:4014–27.
39. Padmanaban V, Keller I, Seltzer ES, Ostendorf BN, Kerner Z, Tavazoie SF. Neuronal substance P drives metastasis through an extracellular RNA-TLR7 axis. Nature. 2024;633:207–15.
40. Magnon C, Hall SJ, Lin J, Xue X, Gerber L, Freedland SJ, Frenette PS. Autonomic nerve development contributes to prostate cancer progression. Science. 2013;341:1236361.
41. Zeng Q, Michael IP, Zhang P, Saghafinia S, Knott G, Jiao W, McCabe BD, Galvan JA, Robinson HPC, Zlobec I, et al. Synaptic proximity enables NMDAR signalling to promote brain metastasis. Nature. 2019;573:526–31.
42. Venkataramani V, Yang Y, Schubert MC, Reyhan E, Tetzlaff SK, Wissmann N, Botz M, Soyka SJ, Beretta CA, Pramatarov RL, et al. Glioblastoma hijacks neuronal mechanisms for brain invasion. Cell. 2022;185(2899–2917): e2831.
43. Winkler F, Venkatesh HS, Amit M, Batchelor T, Demir IE, Deneen B, Gutmann DH, Hervey-Jumper S, Kuner T, Mabbott D, et al. Cancer neuroscience: State of the field, emerging directions. Cell. 2023;186:1689–707.
44. Zhang Z, Lei A, Xu L, Chen L, Chen Y, Zhang X, Gao Y, Yang X, Zhang M, Cao Y. Similarity in gene-regulatory networks suggests that cancer cells share characteristics of embryonic neural cells. J Biol Chem. 2017;292:12842–59.
45. Qu F, Brough SC, Michno W, Madubata CJ, Hartmann GG, Puno A, Drainas AP, Bhattacharya D, Tomasich E, Lee MC, et al. Crosstalk between small-cell lung cancer cells and astrocytes mimics brain development to promote brain metastasis. Nat Cell Biol. 2023;25:1506–19.
46. Gupta PB, Fillmore CM, Jiang G, Shapira SD, Tao K, Kuperwasser C, Lander ES. Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells. Cell. 2011;146:633–44.
47. Zhang D, Park D, Zhong Y, Lu Y, Rycaj K, Gong S, Chen X, Liu X, Chao HP, Whitney P, et al. Stem cell and neurogenic gene-expression profiles link prostate basal cells to aggressive prostate cancer. Nat Commun. 2016;7:10798.

48. Meyer J, Yu K, Luna-Figueroa E, Deneen B, Noebels J. Glioblastoma disrupts cortical network activity at multiple spatial and temporal scales. Nat Commun. 2024;15:4503.
49. Monje M, Borniger JC, D'Silva NJ, Deneen B, Dirks PB, Fattahi F, Frenette PS, Garzia L, Gutmann DH, Hanahan D, et al. Roadmap for the Emerging Field of Cancer Neuroscience. Cell. 2020;181:219–22.
50. Yu K, Lin CJ, Hatcher A, Lozzi B, Kong K, Huang-Hobbs E, Cheng YT, Beechar VB, Zhu W, Zhang Y, et al. PIK3CA variants selectively initiate brain hyperactivity during gliomagenesis. Nature. 2020;578:166–71.
51. Faulkner S, Jobling P, March B, Jiang CC, Hondermarck H. Tumor Neurobiology and the War of Nerves in Cancer. Cancer Discov. 2019;9:702–10.
52. Zhang Y, Lin C, Liu Z, Sun Y, Chen M, Guo Y, Liu W, Zhang C, Chen W, Sun J, et al. Cancer cells co-opt nociceptive nerves to thrive in nutrient-poor environments and upon nutrient-starvation therapies. Cell Metab. 2022;34(1999–2017): e1910.
53. Venkatesh HS, Morishita W, Geraghty AC, Silverbush D, Gillespie SM, Arzt M, Tam LT, Espenel C, Ponnuswami A, Ni L, et al. Electrical and synaptic integration of glioma into neural circuits. Nature. 2019;573:539–45.
54. Costa PAC, Silva WN, Prazeres P, Picoli CC, Guardia GDA, Costa AC, Oliveira MA, Guimaraes PPG, Goncalves R, Pinto MCX, et al. Chemogenetic modulation of sensory neurons reveals their regulating role in melanoma progression. Acta Neuropathol Commun. 2021;9:183.
55. Hu J, Chen W, Shen L, Chen Z, Huang J. Crosstalk between the peripheral nervous system and breast cancer influences tumor progression. Biochim Biophys Acta Rev Cancer. 2022;1877: 188828.
56. Rosas-Ballina M, Olofsson PS, Ochani M, Valdes-Ferrer SI, Levine YA, Reardon C, Tusche MW, Pavlov VA, Andersson U, Chavan S, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011;334:98–101.
57. Reel JM, Abbadi J, Cox MA. T cells at the interface of neuroimmune communication. J Allergy Clin Immunol. 2024;153:894–903.
58. Renz BW, Tanaka T, Sunagawa M, Takahashi R, Jiang Z, Macchini M, Dantes Z, Valenti G, White RA, Middelhoff MA, et al. Cholinergic Signaling via Muscarinic Receptors Directly and Indirectly Suppresses Pancreatic Tumorigenesis and Cancer Stemness. Cancer Discov. 2018;8:1458–73.
59. Liu C, Yang Y, Chen C, Li L, Li J, Wang X, Chu Q, Qiu L, Ba Q, Li X, Wang H. Environmental eustress modulates beta-ARs/CCL2 axis to induce anti-tumor immunity and sensitize immunotherapy against liver cancer in mice. Nat Commun. 2021;12:5725.
60. Dubeykovskaya Z, Si Y, Chen X, Worthley DL, Renz BW, Urbanska AM, Hayakawa Y, Xu T, Westphalen CB, Dubeykovskiy A, et al. Neural innervation stimulates splenic TFF2 to arrest myeloid cell expansion and cancer. Nat Commun. 2016;7:10517.
61. Anderson NM, Simon MC. The tumor microenvironment. Curr Biol. 2020;30:R921–5.
62. Jayaram MA, Phillips JJ. Role of the Microenvironment in Glioma Pathogenesis. Annu Rev Pathol. 2024;19:181–201.
63. Yaniv D, Mattson B, Talbot S, Gleber-Netto FO, Amit M. Targeting the peripheral neural-tumour microenvironment for cancer therapy. Nat Rev Drug Discov. 2024;23:780–96.
64. Gysler SM, Drapkin R. Tumor innervation: peripheral nerves take control of the tumor microenvironment. J Clin Invest. 2021;131:e147276.
65. Chen J, Lai X, Song Y, Su X. Neuroimmune recognition and regulation in the respiratory system. Eur Respir Rev. 2024;33:240008.
66. Wang L, Ge J, Han H, Jia Y, Qin Y. Crosstalk between the nervous system and tumor microenvironment: Functional aspects and potential therapeutic strategies. Cancer Lett. 2024;594: 216986.
67. Cui K, Chen W, Cao R, Xie Y, Wang P, Wu Y, Wang Y, Qin J. Brain organoid-on-chip system to study the effects of breast cancer derived exosomes on the neurodevelopment of brain. Cell Regen. 2022;11:7.
68. Parkin J, Cohen B. An overview of the immune system. Lancet. 2001;357:1777–89.
69. Bassett DS, Sporns O. Network neuroscience. Nat Neurosci. 2017;20:353–64.
70. Khanmammadova N, Islam S, Sharma P, Amit M. Neuro-immune interactions and immuno-oncology. Trends. Cancer. 2023;9:636–49.
71. Jin H, Li M, Jeong E, Castro-Martinez F, Zuker CS. A body-brain circuit that regulates body inflammatory responses. Nature. 2024;630:695–703.
72. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve–an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000;52:595–638.
73. Huang S, Ziegler CGK, Austin J, Mannoun N, Vukovic M, Ordovas-Montanes J, Shalek AK, von Andrian UH. Lymph nodes are innervated by a unique population of sensory neurons with immunomodulatory potential. Cell. 2021;184(441–459): e425.
74. Cole SW, Nagaraja AS, Lutgendorf SK, Green PA, Sood AK. Sympathetic nervous system regulation of the tumour microenvironment. Nat Rev Cancer. 2015;15:563–72.
75. Thapa S, Cao X. Nervous regulation: beta-2-adrenergic signaling in immune homeostasis, cancer immunotherapy, and autoimmune diseases. Cancer Immunol Immunother. 2023;72:2549–56.
76. Mohammadpour H, MacDonald CR, Qiao G, Chen M, Dong B, Hylander BL, McCarthy PL, Abrams SI, Repasky EA. beta2 adrenergic receptor-mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells. J Clin Invest. 2019;129:5537–52.
77. Dutta P, Courties G, Wei Y, Leuschner F, Gorbatov R, Robbins CS, Iwamoto Y, Thompson B, Carlson AL, Heidt T, et al. Myocardial infarction accelerates atherosclerosis. Nature. 2012;487:325–9.
78. Campbell JP, Karolak MR, Ma Y, Perrien DS, Masood-Campbell SK, Penner NL, Munoz SA, Zijlstra A, Yang X, Sterling JA, Elefteriou F. Stimulation of host bone marrow stromal cells by sympathetic nerves promotes breast cancer bone metastasis in mice. PLoS Biol. 2012;10: e1001363.
79. Yaman I, Agac Cobanoglu D, Xie T, Ye Y, Amit M. Advances in understanding cancer-associated neurogenesis and its implications on the neuroimmune axis in cancer. Pharmacol Ther. 2022;239: 108199.
80. Hou Y, Lin B, Xu T, Jiang J, Luo S, Chen W, Chen X, Wang Y, Liao G, Wang J, et al. The neurotransmitter calcitonin gene-related peptide shapes an immunosuppressive microenvironment in medullary thyroid cancer. Nat Commun. 2024;15:5555.
81. Balood M, Ahmadi M, Eichwald T, Ahmadi A, Majdoubi A, Roversi K, Roversi K, Lucido CT, Restaino AC, Huang S, et al. Nociceptor neurons affect cancer immunosurveillance. Nature. 2022;611:405–12.
82. Li F, He C, Yao H, Zhao Y, Ye X, Zhou S, Zou J, Li Y, Li J, Chen S, et al. Glutamate from nerve cells promotes perineural invasion in pancreatic cancer by regulating tumor glycolysis through HK2 mRNA-m6A modification. Pharmacol Res. 2023;187: 106555.
83. Zheng Y, Li L, Shen Z, Wang L, Niu X, Wei Y, Sun S, Zhao J. Mechanisms of neural infiltration-mediated tumor metabolic reprogramming impacting immunotherapy efficacy in non-small cell lung cancer. J Exp Clin Cancer Res. 2024;43:284.
84. James JM, Mukouyama YS. Neuronal action on the developing blood vessel pattern. Semin Cell Dev Biol. 2011;22:1019–27.
85. Shalabi S, Belayachi A, Larrivee B. Involvement of neuronal factors in tumor angiogenesis and the shaping of the cancer microenvironment. Front Immunol. 2024;15:1284629.
86. Larrivee B, Freitas C, Suchting S, Brunet I, Eichmann A. Guidance of vascular development: lessons from the nervous system. Circ Res. 2009;104:428–41.
87. Zahalka AH, Arnal-Estape A, Maryanovich M, Nakahara F, Cruz CD, Finley LWS, Frenette PS. Adrenergic nerves activate an angio-metabolic switch in prostate cancer. Science. 2017;358:321–6.
88. Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu C, Jennings NB, Armaiz-Pena G, Bankson JA, Ravoori M, et al. Author Correction: Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med. 2021;27:2246.
89. Walsh EM, Kim R, Del Valle L, Weaver M, Sheffield J, Lazarovici P, Marcinkiewicz C. Importance of interaction between nerve growth factor and alpha9beta1 integrin in glial tumor angiogenesis. Neuro Oncol. 2012;14:890–901.
90. Kuol N, Stojanovska L, Apostolopoulos V, Nurgali K. Role of the Nervous System in Tumor Angiogenesis. Cancer Microenviron. 2018;11:1–11.
91. Lam CT, Yang ZF, Lau CK, Tam KH, Fan ST, Poon RT. Brain-derived neurotrophic factor promotes tumorigenesis via induction of neovascularization: implication in hepatocellular carcinoma. Clin Cancer Res. 2011;17:3123–33.
92. Chopin V, Lagadec C, Toillon RA, Le Bourhis X. Neurotrophin signaling in cancer stem cells. Cell Mol Life Sci. 2016;73:1859–70.
93. Zhao CM, Hayakawa Y, Kodama Y, Muthupalani S, Westphalen CB, Andersen GT, Flatberg A, Johannessen H, Friedman RA, Renz BW, et al.

Denervation suppresses gastric tumorigenesis. Sci Transl Med. 2014; 6:250ra115.
94. Bernstock JD, Johnston BR, Friedman GK, Chiocca EA, Langer R, Srinivasan SS. Leveraging next generation materials for cancer neuroscience therapies in the central nervous system. Nat Rev Mater. 2024;9:298–300.
95. Cao Y, Ge X, Zhu X, Han Y, Wang P, Akakuru OU, Wu A, Li J. Transformable Neuropeptide Prodrug with Tumor Microenvironment Responsiveness for Tumor Growth and Metastasis Inhibition of Triple-Negative Breast Cancer. Adv Sci (Weinh). 2023;10: e2300545.
96. Yin T, Wang G, Wang L, Mudgal P, Wang E, Pan CC, Alexander PB, Wu H, Cao C, Liang Y, et al. Breaking NGF-TrkA immunosuppression in melanoma sensitizes immunotherapy for durable memory T cell protection. Nat Immunol. 2024;25:268–81.
97. Hayakawa Y, Sakitani K, Konishi M, Asfaha S, Niikura R, Tomita H, Renz BW, Tailor Y, Macchini M, Middelhoff M, et al. Nerve Growth Factor Promotes Gastric Tumorigenesis through Aberrant Cholinergic Signaling. Cancer Cell. 2017;31:21–34.
98. Zhang W, He R, Yang W, Zhang Y, Yuan Q, Wang J, Liu Y, Chen S, Zhang S, Zhang W, et al. Autophagic Schwann cells promote perineural invasion mediated by the NGF/ATG7 paracrine pathway in pancreatic cancer. J Exp Clin Cancer Res. 2022;41:48.
99. Contreras-Zarate MJ, Day NL, Ormond DR, Borges VF, Tobet S, Gril B, Steeg PS, Cittelly DM. Estradiol induces BDNF/TrkB signaling in triple-negative breast cancer to promote brain metastases. Oncogene. 2019;38:4685–99.
100. Pan Y, Hysinger JD, Barron T, Schindler NF, Cobb O, Guo X, Yalcin B, Anastasaki C, Mulinyawe SB, Ponnuswami A, et al. NF1 mutation drives neuronal activity-dependent initiation of optic glioma. Nature. 2021;594:277–82.
101. Li J, Zhu S, Kozono D, Ng K, Futalan D, Shen Y, Akers JC, Steed T, Kushwaha D, Schlabach M, et al. Genome-wide shRNA screen revealed integrated mitogenic signaling between dopamine receptor D2 (DRD2) and epidermal growth factor receptor (EGFR) in glioblastoma. Oncotarget. 2014;5:882–93.
102. Zuo S, Wang Z, Jiang X, Zhao Y, Wen P, Wang J, Li J, Tanaka M, Dan S, Zhang Y, Wang Z. Regulating tumor innervation by nanodrugs potentiates cancer immunochemotherapy and relieve chemotherapy-induced neuropathic pain. Biomaterials. 2024;309: 122603.
103. Gao D, Fang L, Liu C, Yang M, Yu X, Wang L, Zhang W, Sun C, Zhuang J. Microenvironmental regulation in tumor progression: Interactions between cancer-associated fibroblasts and immune cells. Biomed Pharmacother. 2023;167: 115622.
104. McCollum SE, Shah YM. Stressing Out Cancer: Chronic Stress Induces Dysbiosis and Enhances Colon Cancer Growth. Cancer Res. 2024;84:645–7.
105. Redding A, Grabocka E. Stress granules and hormetic adaptation of cancer. Trends Cancer. 2023;9:995–1005.
106. Sarkar DK, Murugan S, Zhang C, Boyadjieva N. Regulation of cancer progression by beta-endorphin neuron. Cancer Res. 2012;72:836–40.
107. Jiang SH, Hu LP, Wang X, Li J, Zhang ZG. Neurotransmitters: emerging targets in cancer. Oncogene. 2020;39:503–15.
108. Globig AM, Zhao S, Roginsky J, Maltez VI, Guiza J, Avina-Ochoa N, Heeg M, Araujo Hoffmann F, Chaudhary O, Wang J, et al. The beta(1)-adrenergic receptor links sympathetic nerves to T cell exhaustion. Nature. 2023;622:383–92.
109. Chen M, Qiao G, Hylander BL, Mohammadpour H, Wang XY, Subjeck JR, Singh AK, Repasky EA. Adrenergic stress constrains the development of anti-tumor immunity and abscopal responses following local radiation. Nat Commun. 1821;2020:11.
110. Chang A, Botteri E, Gillis RD, Lofling L, Le CP, Ziegler AI, Chung NC, Rowe MC, Fabb SA, Hartley BJ, et al. Beta-blockade enhances anthracycline control of metastasis in triple-negative breast cancer. Sci Transl Med. 2023;15:eadf1147.
111. Tu RH, Wu SZ, Huang ZN, Zhong Q, Ye YH, Zheng CH, Xie JW, Wang JB, Lin JX, Chen QY, et al. Neurotransmitter Receptor HTR2B Regulates Lipid Metabolism to Inhibit Ferroptosis in Gastric Cancer. Cancer Res. 2023;83:3868–85.
112. Guo X, Qiu W, Li B, Qi Y, Wang S, Zhao R, Cheng B, Han X, Du H, Pan Z, et al. Hypoxia-Induced Neuronal Activity in Glioma Patients Polarizes Microglia by Potentiating RNA m6A Demethylation. Clin Cancer Res. 2024;30:1160–74.
113. Bannwarth B, Kostine M. Nerve Growth Factor Antagonists: Is the Future of Monoclonal Antibodies Becoming Clearer? Drugs. 2017;77:1377–87.
114. Qin J, Liu J, Wei Z, Li X, Chen Z, Li J, Zheng W, Liu H, Xu S, Yong T, et al. Targeted intervention in nerve-cancer crosstalk enhances pancreatic cancer chemotherapy. Nat Nanotechnol. 2024. https://doi.org/10.1038/s41565-024-01803-1.
115. Tang Q, Zhao G, Fang H, Jiang Y, Ma P, Zhou J, Liu D, Xing S, Li G, Liu N, et al. Nanoparticle drug delivery system for the treatment of brain tumors: Breaching the blood-brain barrier. Acta Pharm Sin B. 2024;14:2786–9.

Publisher's Note