



Mini Review

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Neuronal Infiltration in the Tumor Microenvironment: Cellular Sources, Neuro-Immune Crosstalk, and Therapeutic Implications

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Abstract

The nervous system actively participates in tumor initiation, progression, and immune evasion. Tumor cells and stromal cells secrete neurotrophic factors and axon guidance molecules to recruit sensory, sympathetic, and parasympathetic nerve fibers into the tumor microenvironment, while also inducing the migration and differentiation of neural progenitor cells derived from the central nervous system. Schwann cells function as a “bridge” between nerves and tumors, driving perineural invasion. Tumor-infiltrating neurons systematically reprogram immune cell function via the secretion of neurotransmitters and neuropeptides. These regulatory effects are highly context-dependent: the same neurotransmitter can elicit distinct outcomes based on the receptor expression profile of the local microenvironment. Therapeutic strategies targeting the neuro-immune axis have demonstrated promising potential in preclinical models for improving the efficacy of immunotherapy. Nevertheless, multiple challenges including the absence of cell subtype-specific research tools, inherent limitations of existing experimental model systems, and the shortage of clinically actionable biomarkers remain major barriers to clinical translation. Future research should integrate spatial multi-omics technologies with in vivo functional validation to decipher the dominant neural regulatory programs in specific cancer types, thereby facilitating the development of precise combination therapies that integrate neural modulation with immune checkpoint blockade.

Keywords: Tumor Neuroscience, Nerve Infiltration, Neuroimmune Crosstalk, Tumor Microenvironment, Immunotherapy Resistance

Abbreviations: Ach: acetylcholine; ARTN: artemin; ADRB2: beta-2 adrenergic receptor; CAFs: cancer-associated fibroblasts; CGRP: calcitonin gene-related peptide; CRC colorectal cancer; CHRM1: cholinergic receptor, muscarinic 1; CNS: central nervous system; DC: dendritic cell; MDSCs: myeloid-derived suppressor cells; NE: norepinephrine; NK: natural killer; NMB: Neuromedin B; NTs: neurotrophins; PCA: prostate cancer; PDAC: pancreatic ductal adenocarcinoma; PNI: perineural invasion; PNS: peripheral nervous system; PSNS: parasympathetic nervous system; sEVs: small extracellular vesicles; SNS: sympathetic nervous system; SVZ: subventricular zone; SP: substance P; TAMs: tumor-associated macrophages; TME: tumor microenvironment; TNBC: triple-negative breast cancer; Treg regulatory T cells; Trk: tropomyosin receptor kinase; GDNF: Glial cell line-derived neurotrophic factor; G-CSF: granulocyte colony-stimulating factor

Introduction

The nervous system serves as the dominant regulatory system of the human body. It forms an interconnected network via neurons and glial cells, which undertakes the functions of integrating sensory input, coordinating organ activities, maintaining homeostasis, and mediating responses to environmental changes. For a long time, nerves have been regarded as quiescent bystanders in cancer progression. Recent studies have demonstrated that nerves are not passive components, but rather active participants in cancer progression [1]. Neurons of the autonomic nervous system not only modulate tumor initiation and progression via the secretion of neurotransmitters and neurotrophic factors [2-4], but also have been demonstrated to drive remodeling of the tumor immune microenvironment and modulate antitumor immune responses [5]. This review aims to synthesize existing findings, identify current limitations in the development of tumor-associated neural research, and delineate emerging directions for anti-tumor immunotherapy targeting intratumoral neuromodulation.

Sources and Classification of Tumor-Infiltrating Neurons

Nerves detected within tumors can originate from two distinct pathways: neurogenesis, which refers to the invasion of tumors by nerves, and perineural invasion, which refers to the invasion of nerves by tumor cells. An intact endogenous innervation network is already established in the host tissue prior to tumor onset. Following malignant cell transformation, axons that are normally distributed in the native tissue are either hijacked or passively encapsulated by tumor cells, and are subsequently incorporated into the intratumoral nerve fiber network [6]. These nerve fibers, which originally innervate blood vessels, glands and other structures in normal tissues, can be co-opted by tumor cells to act as “supporting elements” for tumor proliferation within the tumor microenvironment [7, 8]. After tumorigenesis, tumor cells can either induce peripheral nerve invasion or recruit distal neural progenitor cells for redomestication. Specifically, tumor cells actively induce adjacent nerve fibers to invade the tumor mass and form new axonal branches via secreting neurotrophic factors (including NGF, BDNF, NT-3 and NT-4) and axon guidance molecules [9, 10]. Analogous to the mechanism through which tumors induce angiogenesis, studies focusing on prostate cancer (PCa) [11] and pancreatic cancer [12] have demonstrated that tumors can innervate the Tumor Microenvironment (TME) by recruiting nerve fibers in a manner similar to how they recruit blood vessels [13, 14]. In PCa, central nervous system progenitor cells can egress from the Subventricular Zone (SVZ), cross the blood-brain barrier, migrate to the tumor site via the systemic circulation, and terminally differentiate into mature adrenergic neurons within the TME [11].

Perineural Invasion (PNI) is defined as the migration of tumor cells along nerve sheaths, a process that promotes cancer

proliferation and correlates with adverse patient prognosis [12, 15]. The incidence of perineural invasion in pancreatic ductal adenocarcinoma reaches 74%, which is significantly higher than that of other tumor types. PNI is hypothesized to be the primary pathway for extrapancreatic spread of PDAC, and exosome-mediated metastasis in Colorectal Cancer (CRC) is considered to be closely associated with PNI [16].

Additionally, bone marrow-derived mesenchymal stem cells have the potential to differentiate into neurons under specific induction conditions, thus representing a promising alternative source of neurons within TME. However, this research direction remains underexplored to date.

Mechanisms of Neuronal Recruitment and Infiltration

Neural invasion within tumor tissue is not a passive process; rather, it arises from the active hijacking of neurodevelopmental programs by tumor cells. Tumor cells synergize with stromal components to drive neurite ingrowth into the TME via secreting Neurotrophins (NTs) and axon guidance molecules. This process involves two primary patterns: axonogenesis, defined as the extension of pre-existing nerve axons into tumor tissue, and neurogenesis, which encompasses the migration and differentiation of neural progenitor cells.

Molecular Signaling Level: Neurotrophic Factors and Axon Guidance Molecules

NTs including NGF, BDNF, Neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5), constitute the core molecular family mediating nerve recruitment by tumors [17]. Through autocrine- and paracrine-secreted NTs and axon guidance molecules, tumor cells activate Tropomyosin Receptor Kinase (Trk) receptors at peripheral nerve terminals, which subsequently promotes axon sprouting and elongation via the downstream PI3K, Ras, and PLC signaling pathways [18]. Neuromedin B (NMB) secreted by cervical cancer cells activates the Schwann cell receptor NMBR, which induces axonal regeneration and PNI via opening T-type calcium channels and activating the PKA signaling pathway [19].

Glial cell line-Derived Neurotrophic Factor (GDNF) and its receptor complex RET/GFR α play a critical role in PNI [20]. Both neurons and Schwann Cells (SCs) secrete GDNF and Artemin (ARTN). Upon binding to the RET/GFR α receptor complex, tumor cells consequently exhibit enhanced adhesion and invasion capabilities [21]. Additionally, Granulocyte Colony-Stimulating Factor (G-CSF) has been confirmed to exert neurotrophic effects and promote nerve growth in mouse models of PCa [5]. Accordingly, the detection and quantification of neurotrophic growth factors that drive tumor axonogenesis may provide diagnostic or prognostic clinical value [2, 22] (Table 1).

Table 1: Neurotrophins and axon guidance molecules are involved in the regulation of tumor nerve invasion.

Types of Cancer	NTs	Neural modulation mechanisms	Classification of Nerves	Impact on Tumor Biology
Prostatic Cancer	proNGF/NGF	Cancer cells secrete proNGF, which activates neuronal TrkA to drive axonal outgrowth and neural invasion.	Sensory Nerve	a statistically significant positive association with high-risk PCa [23]
Prostatic Cancer	G-CSF	Neuron-derived DKK1 promotes MDSC infiltration and contributes to T lymphocyte suppression.	Parasympathetic Nerve	Contribute to the development and progression of PCa; inhibit T-cell activity [24].
Gastric Cancer	NGF	Gastric cancer cells secrete NGF to induce parasympathetic innervation, and promote cancer cell proliferation via cholinergic regulation of the WNT signaling pathway.	Parasympathetic Nerve	The maturation and antigen presentation of DCs were impaired, which in turn suppressed the cytotoxic activity of antitumor T cells and ultimately promoted the progression of gastric cancer [25].
Gastric Cancer	CGRP	Activation of the Rb-E2F pathway promotes the in vivo growth of gastric tumors.	Sensory Nerve	Contributes to the pathogenesis of gastric cancer [26]
Pancreatic Cancer	NGF and BDNF	The upregulation of NGF and BDNF initiates a feed-forward regulatory loop that promotes sympathetic hyperinnervation and elevates local norepinephrine concentrations.	Sympathetic Nerve	It suppresses the cytotoxic activity of NK cells, thereby facilitating tumor immune escape and neoplastic growth, and contributes to resistance against immunotherapy [9].
Pancreatic Cancer	LIF	It promotes the differentiation and migration of SCs via activation of the JAK/STAT3/AKT signaling axis, and also induces an increase in both the number of neurites and the soma area of dorsal root ganglion neurons.	SC-mediated neural remodeling; sensory nerves (dorsal root ganglia)	Increase in neural density associated with PDAC [27]
Breast Cancer	NGF	NGF is overexpressed in cancer cells, leading to enhanced sympathetic innervation density and neuronal activity.	Sympathetic nervous system (β 2-adrenergic signaling)	Contributes to the progression of breast cancer and diminishes the therapeutic efficacy of both immunotherapy and chemotherapy.
Colorectal Cancer	NGF	The molecular and cellular mechanisms underlying axonogenesis have yet to be fully elucidated.	Parasympathetic nervous system (mediated by cholinergic neurons)	NGF-mediated cholinergic innervation may promote colorectal carcinogenesis; CHRM3 activation facilitates intestinal tumorigenesis in vivo.
Colorectal Cancer	NPCs and NPY	Norepinephrine activates β -adrenergic signaling	Sympathetic Nerve	Promotes colorectal cancer metastasis [28]; mediates cell proliferation and angiogenesis [29]
Cervical Cancer	NGF and BDNF	NGF promotes epithelial-mesenchymal transition (EMT) via activation of the Hippo/YAP signaling pathway; likewise, BDNF-mediated activation of the TrkB pathway contributes synergistically to this process.		Proliferation and migration of cervical cancer cells [30]
Cervical Cancer	NT3 and GDNF	HGF/c-Met pathway, mTOR/NGF pathway, NF- κ B pathway and MAPK pathway		Facilitate perineural invasion and migration of cancer cells [31]

Note*: BDNF: brain-derived neurotrophic factor; CGRP: Calcitonin Gene-Related Peptide; G-CSF: granulocyte colony-stimulating factor; GDNF: Glial cell-derived neurotrophic factor; LIF: leukemia inhibitory factor; NGF: nerve growth factor; NPY: Nerve Peptide Y; NT3: Neurotrophic factor-3

Axon guidance molecules, including Semaphorin, Netrin, Slit, and Ephrin, were originally identified to mediate axonal attraction or repulsion during nervous system development. However, they are extensively reactivated and exert critical functions in tumors, acting as key mediators of tumor-nerve crosstalk [5, 32].

Tumor-derived exosomes (small extracellular vesicles, sEVs) represent a newly identified mechanism underlying neural recruitment reported in recent years. Carrying multiple biological cargos including DNA, RNA, miRNA, lipids and proteins, sEVs promote neural invasion by facilitating neurite outgrowth and

driving potential nerve fiber reprogramming [33]. p75NTR present in sEVs isolated from plasma of patients with PDAC induces dedifferentiation of SCs and promotes their migratory capacity [34].

Cellular Mediators: Synergistic Interactions between Schwann Cells and Immune Cells

SCs are the primary supporting glial cells of the Peripheral Nervous System (PNS). They ensheath the axons of peripheral nerves and execute a wide range of critical functions, including mediating

rapid signal transduction, maintaining nerve homeostasis, synthesizing extracellular matrix, regulating neurogenesis and supporting nerve regeneration. SCs also serve as a core “bridge” in modulating immunity during tumor neural invasion [35]. A paracrine positive feedback loop exists between Schwann cells and Tumor-Associated Macrophages (TAMs). In Pancreatic Ductal Adenocarcinoma (PDAC), TAM-activated SCs secrete IL-33 to recruit TAMs to the perineural microenvironment and drive polarization of TAMs toward the pro-tumorigenic M2 phenotype [36]. Immune cells are not merely passive responders, but are actively involved in neural recruitment. In PDAC, inflammatory monocytes are recruited to the nerve injury site by CCL2 secreted by SCs, and promote PNI via the expression of Cathepsin B [37]. Additionally, gastrointestinal malignancies can drive the generation of intratumoral neurons from enteric neural progenitor cells.

Perineural Invasion: Neural Recruitment and Intratumoral invasion

Perineural invasion (PNI) is defined as the invasion of tumor cells into the nerve sheath and/or encircling more than 33% of the nerve perimeter, and represents a manifestation of nerve remodeling. PNI is a biological feature of multiple malignant tumors, and is often significantly associated with tumor invasion, metastasis, cancer-related pain and poor clinical prognosis [38]. The molecular mechanism underlying PNI involves the crosstalk and cooperation of multiple signaling pathways. In PDAC, PNI-associated Cancer-Associated Fibroblasts (pCAFs) facilitate the formation of a hyperlactate-enriched tumor microenvironment, while concomitantly promoting the perineural invasion capacity of pancreatic cancer cells [39]. Extracellular vesicle-mediated delivery of non-coding RNA transcripts associated with PNI to pancreatic cancer cells modulates YBX1-dependent m⁵C RNA methylation, thereby facilitating perineural invasion [40]. N4-acetylcytidine-modified ITGB5 mRNA enhances perineural invasion in pancreatic ductal adenocarcinoma through a NAT10-dependent mechanism [41]. Activation of the β 2-adrenergic receptor by catecholamines upregulates the secretion of NGF and BDNF in PDAC cells, ultimately driving the development of PNI [42].

SCs secrete GDNF, NGF and BDNF, and specifically activate receptor tyrosine kinase family members (including RET, TrkA, and TrkB) on the surface of tumor cells, thereby guiding tumor cell migration along nerves [43-45]. IL-6 secreted by SCs activates STAT3 signaling in cancer cells to promote PNI in PDAC. Meanwhile, the expression and secretion of NPY acts on NPY1R to activate ERK and Smad2 signaling, which synergistically promotes PNI in oral squamous cell carcinoma in conjunction with TGF β signaling [46, 47].

Tumor cells that develop PNI utilize the perineural space as a low-resistance channel to circumvent conventional lymphatic and vascular barriers for long-distance dissemination, and can even metastasize to the central nervous system [21]. PNI serves as a robust negative prognostic biomarker, which is significantly correlated with elevated tumor recurrence rates, reduced overall

survival and severe refractory neuropathic pain.

Neuro-Immune Crosstalk in the Tumor Microenvironment

Neuroimmune crosstalk within the TME represents one of the core mechanisms underlying tumor progression and immune escape. Tumor cells actively recruit peripheral nerves, remodel neural circuitry, and systematically modulate immune cell function via neurochemical signaling-including neurotransmitters and neuropeptides-thereby fostering an immunosuppressive TME. During immune surveillance, neural signals also inhibit natural killer cells (NK cells) and T cells from secreting tumoricidal factors and mediating contact-dependent killing of tumor cells. Sympathetic signaling and neuropeptides such as CGRP can promote the polarization of TAMs toward the M2-type tumor-promoting phenotype, which in turn supports tumor progression and immunosuppression. This process additionally impairs the maturation of dendritic cells and promotes the accumulation of myeloid-derived suppressor cells (MDSCs) in the TME, ultimately attenuating the capacity of these antigen-presenting cells to initiate antitumor T-cell responses [48, 49].

Neurotransmitters: The “Chemical Language” of Immune Regulation

Through the release of classical neurotransmitters, neurons can directly communicate with immune cells that express the corresponding neurotransmitter receptors, and the downstream effects are highly dependent on the receptor subtype and cellular context.

Sympathetic (adrenergic) signaling mediated by norepinephrine: Adrenergic signaling constitutes a direct mechanistic pathway through which sympathetic nervous system activation modulates the lung TME and facilitates immune evasion [50]. T cells are capable of synthesizing Acetylcholine (ACh) upon stimulation by Norepinephrine (NE), thereby establishing a bidirectional NE-ACh signaling axis [51]. Clinical studies have revealed that circulating NE levels in patients with lung adenocarcinoma are positively correlated with a poor therapeutic response to anti-PD-1 immunotherapy, indicating that adrenergic signaling contributes to immune checkpoint tolerance. Mechanistic investigations demonstrated that NE signaling in tumor cells concurrently suppresses CXCL9 expression-a key chemokine required for CD8⁺ T cell recruitment-and enhances extracellular adenosine production, a well-established immunosuppressive metabolite. Collectively, these alterations impair CD8⁺ T cell infiltration into the TME and compromise their effector function, thereby contributing to resistance against immunotherapy [52]. Furthermore, the binding of NA to the β 2-adrenergic receptor (ADRB2) expressed on immune cells not only suppresses cytokine production and cell proliferation [53], but also inhibits the antitumor cytotoxic activity of CD8⁺ T cells [54]. Additionally, this process can suppress the activity of NK cells and facilitate the recruitment and accumulation of MDSCs [55].

Parasympathetic Cholinergic Signaling (ACh): The relationship exhibits bidirectional effects [56]. On the one hand, ACh released from vagal nerve terminals enhances anti-tumor immunity via activation of $\alpha 7$ nicotinic acetylcholine receptors [57]. On the other hand, tumor antigen-stimulated CD4⁺ T cells upregulate choline acetyltransferase, enabling autocrine ACh production, which modulates intracellular calcium signaling and thereby mitigates T cell exhaustion [58]. ACh in PDAC activates T cells to inhibit tumor proliferation and invasion, which reveals the potential anti-tumor function of the vagus nerve [59]. ACh from the vagus nerve inhibits the activity of CD8⁺ T cells via the AChR CHRM3, and negatively regulates anti-tumor immunity in hepatocellular carcinoma, as supported by prior research [60].

Sensory Neuropeptides (CGRP, substance P): Sensory neurons represent one of the major neuronal subtypes residing in the TME, and CGRP, a neuropeptide secreted by these neurons, exerts a robust immunomodulatory effect. High CGRP expression in oral cancer cells is negatively correlated with the infiltration counts of CD4⁺ T cells, cytotoxic CD8⁺ T cells and NK cells within

the TME [61, 62]. Substance P (SP), a sensory neurotransmitter with established tumor growth-promoting properties, enhances the anti-tumor immune response against PDAC by stimulating pro-inflammatory cytokine synthesis and potentiating NK cell function [63]. Chronic SP release induces “neurogenic inflammation”. On one hand, this process triggers dendritic cell migration and initiates T helper cell differentiation [64]; on the other hand, it promotes tumor progression by inducing M2 polarization of macrophages [65]. SP has been reported to drive T cell depletion in melanoma [66] breast cancer [67, 68], and glioma [69], and to directly regulate cell growth and apoptosis via MAPK activation [70].

Calcitonin Related Peptide (CGRP): Interference targeting T cell receptors inhibits T cell proliferation and cytokine production, while promoting the M2 polarization of macrophages [71]. In Triple-Negative Breast Cancer (TNBC), tumor-derived NGF activates sensory neurons to induce CGRP release; CGRP then acts on CAFs to promote collagen deposition, forming a physical barrier that suppresses immune rejection [72] (Figure 1).

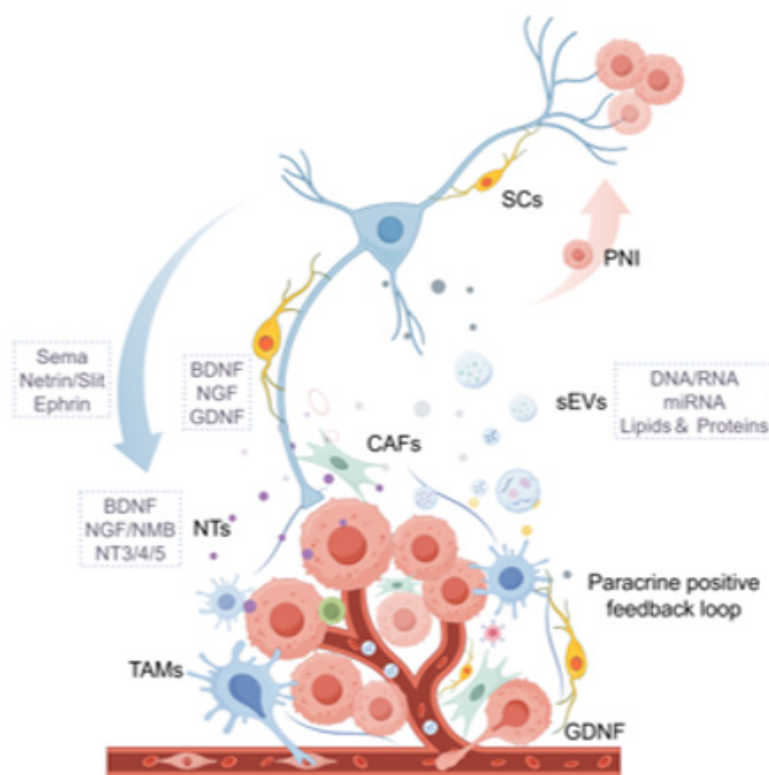


Figure 1: Molecular mediators governing neuro-immune crosstalk in the TME.

“Signal Reversal”: A Double-Edged Sword Dependent on Context

Lymph nodes receive both sympathetic and sensory nerve fibres, but are devoid of parasympathetic innervation. Intratumoral

invasive nerves fulfill a key function in modulating local antitumor immune responses via the regulation of draining lymph nodes. Sympathetic denervation reduces lymphatic vessel area and suppresses the progression of tongue cancer [73]. Studies on

PDAC have demonstrated that p75NTR-carrying sEVs establish pre-metastatic niches in lymph nodes, thereby promoting lymph node metastasis and inducing lymphangiogenesis [74]. To date, the specific scope of crosstalk between cancer type-specific innervation and tumor-draining lymph node innervation remains unclear. Clarifying this interaction is critical for achieving a more comprehensive understanding of the functional roles of nerves in cancer.

“Signal Reversal”: A Double-Edged Sword Dependent on Context

Neuroimmune crosstalk is not simply characterized as “inhibition” or “activation”, but rather exhibits notable context-dependent variability. The phenomenon wherein the identical neurotransmitter can exert opposing effects under different receptor expression backgrounds is termed “sign inversion”. Overexpression of 5-HT_{1a}R in TNBC inhibits epithelial-mesenchymal transition and metastasis via the disruption of TGF- β receptors [75]. In myeloid cells, dopamine signalling through DRD4 suppresses the pro-tumor inflammatory output of TAMs and induces immune remodelling of the TME [76]. Dopamine acts on D1-like receptors to stimulate anti-tumor immunity, while it acts on D2-like receptors to induce immunosuppression; the net effect of dopamine depends on the balance of these receptors [77]. Collectively, these findings indicate that identifying whether the dominant neural signalling program in an individual patient is immunostimulatory or immunosuppressive is the core determinant for developing targeted therapeutic strategies.

Therapeutic Translation: Targeting Neuro-Immune Crosstalk

Currently, targeting neuroimmune crosstalk has emerged as a novel strategy for potentiating cancer immunotherapy. CGRP antagonists, including rimegepant, have demonstrated the capacity to modulate the tumor immune microenvironment in TNBC and enhance the therapeutic efficacy of immunotherapy [72]. β receptor-blocking agent and other pharmacological agents are currently undergoing re-evaluation owing to their demonstrated immunomodulatory properties. Targeting NGF constitutes a promising therapeutic strategy. In preclinical studies, engineered CAR-T cells designed to secrete anti-NGF single-chain variable fragments exhibited enhanced antitumor activity relative to conventional CAR-T cells, largely through inhibition of tumor-associated innervation and subsequent attenuation of catecholamine-mediated immunosuppression [78]. Vagus nerve stimulation enhances anti-tumor immunity through activation of the cholinergic anti-inflammatory pathway-specifically, by augmenting the cytotoxic activity of CD8⁺T cells and NK cells, while concurrently suppressing the immunosuppressive function of MDSCs [55].

Challenges and Future Directions

Although recent research advances have underscored the

central role of neural mechanisms in antitumor therapy, critical gaps remain between the discovery of neural-tumor interactions and the development of effective neurotargeted therapeutics. Neural regulation of tumor immunity is highly context-dependent, necessitating the systematic dissection of dominant receptors and downstream signaling networks in specific cancer types and cell populations. Furthermore, most current interventions targeting intralesional nerves, including chemical ablation and surgical denervation, lack subtype specificity. Broad neuromodulation can concurrently disrupt neural circuits that confer immune support, underscoring the demand for neurotype-specific strategies [79]. To date, however, there remains a dearth of established tools capable of selectively targeting tumor-associated sensory, sympathetic, or parasympathetic subpopulations in vivo.

Neurostructural research enables multiple morphological and histological assessments of human oncology specimens, animal models, tissue cultures and organoids [80-82]. However, morphological analysis of the nerve tumor microenvironment still faces considerable challenges. Human-derived tumor xenograft models lack fully functional innervation. While organoids and organotypic sections retain partial tissue architecture, they lack systemic circulation and intact organ physiological functions, which limits in vivo pharmacodynamic evaluation of neuro-immune crosstalk. Furthermore, the spatial interaction among Schwann cells, neural progenitor cells and immune cells in the microenvironment is difficult to reconstruct in two-dimensional culture systems. Concurrently, insufficient identification of biomarkers for nerve-tumor crosstalk not only severely restricts the capacity of patient stratification and eligibility screening for clinical trial enrollment, but also markedly reduces the comparability between independent studies.

Conclusion

Recent advances in understanding neuroimmune crosstalk in the regulation of cancer progression and the tumor immune microenvironment have laid a foundational foundation for both basic and clinical research in the emerging discipline of cancer neurobiology. This field has established a novel paradigm for developing innovative clinical strategies for cancer diagnosis, prognosis, and treatment. Translating the mechanistic insights of cancer neuromodulation into clinical application represents the next key opportunity and core challenge in the field.

Conflict of Interest

The authors disclosed no conflict of interests.

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