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Boqun Jia, Lingyun Zhao, Muhan Tang, Nanbin Xie, Yunqian Huang, Xiaoxia Liang, Guanhu Yang, Qibiao Wu, Zhiguang Sun, Hiu Yee Kwan, Hao Sun & Keyang Xu

Neuron–Tumor Crosstalk in Cancer: Molecular Mechanisms and Translational Advances

Boqun Jia[1*], Lingyun Zhao[1*], Muhan Tang[1], Nanbin Xie[1], Yunqian Huang[1], Xiaoxia Liang[1], Guanghu Yang[1], Qibiao Wu[1], Zhiguang Sun[1], Hiu Yee Kwan[2,4,5,6#], Hao Sun[3#], Keyang Xu[1#]

[1]Faculty of Chinese Medicine, and State Key Laboratory of Mechanism and Quality of Chinese Medicine, Macau University of Science and Technology, Macau, China.

[2]Center for Cancer & Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, China.

[3]Wolfson Institute for Biomedical Research, UCL Division of Medicine, University College London, Gower St, WC1E 6BT, London, United Kingdom.

[4]Institute of Research and Continuing Education, Hong Kong Baptist University, Shenzhen, China.

[5]HKBU-Musketeers Foundation Traditional Chinese Medicine Research Institute for Age-related Diseases, Hong Kong Baptist University, Hong Kong SAR, China.

[6]Institute of Systems Medicine and Health Sciences, Hong Kong Baptist University, Hong Kong, China.

[*]These authors contributed equally

[#]Correspondence: These authors are co-corresponding authors

Boqun Jia: jiaboqun@yeah.net

Lingyun Zhao: 3250001971@student.must.edu.mo

Muhan Tang: 2250026239@student.must.edu.mo

Nanbin Xie: 2250025803@student.must.edu.mo

Yunqian Huang: 2250028601@student.must.edu.mo

Xiaoxia Liang: 1654886759@qq.com

Guanghu Yang: ghyang@must.edu.mo
Qibiao Wu: qbwu@must.edu.mo
Zhiguang Sun: zgsun@must.edu.mo
Hiu Yee Kwan: hykwan@hkbu.edu.hk
Hao Sun: hao.sun@ucl.ac.uk
Xu K: kyxu@must.edu.mo

Correspondence

Dr. Hiu Yee Kwan
Address: Centre for Cancer & Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, China.
Email: hykwan@hkbu.edu.hk
Dr. Hao Sun
Address: Wolfson Institute for Biomedical Research, UCL Division of Medicine, University College London, Gower St, WC1E 6BT, London, United Kingdom.
Email:hao.sun@ucl.ac.uk
Dr. Keyang Xu
Faculty of Chinese Medicine, and State Key Laboratory of Mechanism and Quality of Chinese Medicine, Macau University of Science and Technology, Macau, China.
Email: kyxu@must.edu.mo

Abstract:

Tumor neuron hijack is a malignant adaptive program whereby tumor cells recruit, physically engage and functionally reprogram the peripheral and central nervous system within the local microenvironment and host macroenvironment; this process not only exploits neuro-immune regulatory machineries, neural endocrine signaling, and nutrient supply for sustaining tumor growth, invasion, metastasis, immune escape and treatment resistance, but also closely involves the induction and amplification of cancer-associated pain, a common and debilitating manifestation of the host's pathological response to tumor-neural crosstalk, which further perturbs the host

macroenvironment and facilitates tumor progression. Neoplastic cells employ context-dependent strategies: central nervous system tumors (e.g., gliomas) integrate into existing neuronal circuits via synaptogenesis and metabolic coupling, while peripheral solid tumors induce de novo innervation via neurotrophic factors, axon guidance cues regulating angiogenesis, and perineural invasion. Sympathetic, parasympathetic, and sensory nerves modulate tumor behavior via neurotransmitters or neuropeptides, with autonomic nerves also regulating endocrine glands to reprogram tumor metabolism. Pivotal to this regulation is the tripartite crosstalk among nerves, immune cells, and tumor cells, which establishes an immunosuppressive tumor microenvironment and drives progression from immune equilibrium to escape. These mechanisms have spurred therapeutic avenues such as neurotrophic agent repurposing, synaptic blockade, and neural-signal reprogramming, particularly in combination with immunotherapy, with promising preclinical and translational potential for precision oncology and cancer pain management.

Keywords: Tumor-neuro crosstalk; tumor immune microenvironment; metabolic plasticity; neuroendocrine axis; neuropathic pain; tumor neuron hijack

1. Introduction

The study of the association between tumors and the nervous system can be traced back over a century (with the earliest morphological descriptions in the 19th century), when the phenomenon of perineural invasion (PNI) was first reported in 1835[1]. Subsequent research has confirmed the existence of bidirectional functional "symbiotic" interactions (reciprocal neurotrophic support and signaling) between tumor cells and neurons, which are strongly correlated with poor patient prognosis, increased recurrence, and metastasis[2,3]. With the advancement of techniques such as

immunohistochemistry (and later single-cell sequencing and spatial transcriptomics), landmark research in 2008 demonstrated through clinical sample analysis that neural density (via cancer-related axonogenesis and neurogenesis) in tumor regions was significantly higher than that in the corresponding healthy tissues[4]. In 2013, another seminal study further validated this through a prostate cancer animal model, showing that blocking neural innervation (sympathetic and parasympathetic) could significantly inhibit tumor growth and metastasis, thereby establishing the nervous system as an essential supporting "ecosystem" factor for tumor survival[5]. These landmark studies propelled the development of cancer neuroscience into an independent, rapidly evolving discipline, overcoming the limitations of traditional tumor research, which overlooked neural contributions.

Traditional tumor research has long centered on the complex interactions among immune cells, angiogenesis, and extracellular matrix. In contrast, despite its essential role as a functional component of the tumor microenvironment (TME), the nervous system has received significantly less attention in cancer research than the immune system. Although clinical observations have long indicated a strong link between neural innervation and tumor progression, this review systematically examines the diverse roles of the nervous system in the TME. It focuses particularly on the tripartite interactions among tumor cells, neural elements, and immune cells while assessing the clinical translational prospects of targeting the neuro-oncology axis[6]. This study addresses the fundamental question of how the nervous system promotes tumor progression via cellular and molecular mechanisms. It outlines three key mechanisms: First, local neural innervation drives tumor growth via sympathetic and sensory nerves and neuroglial tumor synapses. Second, systemic neural influences aggravate metastasis and immunosuppression in settings of chronic stress and autonomic nervous system dysregulation, including a distinct neuroendocrine dimension in which autonomic nerves directly regulate endocrine glands to release

hormones that reprogram tumor metabolism, with cancer-associated neuropathic pain serving as a key driver. Third, targeted interventions along the neuro-oncology axis, such as synaptic inhibitors and neural signal modulation, offer promising therapeutic opportunities and open new avenues for cancer treatment[7,8] (**Table 1**).

2. Neural Recruitment and Signaling in the Tumor Microenvironment

2.1 Overview of Neural Recruitment in Central and Peripheral Tumors

Tumors do not passively receive neural innervation; instead, they actively construct a neural microenvironment that promotes tumor growth. The core mechanism centers on the secretion of chemotactic factors, primarily neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which establish a directional signaling network to recruit nerve fibers[9,10]. In addition to NGF and BDNF, tumor cells can secrete other neuroattractive mediators, including chemokines such as CCL2 and CXCL12, inflammatory cytokines such as IL-6, and additional neurotrophins such as neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5), all of which contribute to neurite attraction and nerve ingrowth. These factors broaden the spectrum of molecular cues that support the establishment of a neuralized TME. These factors bind to tropomyosin receptor kinases (TrkA and TrkB) expressed on neurons and nerve terminals, thereby activating downstream survival and growth cascades (RAS/MAPK/ERK and PI3K/AKT) that drive axonal sprouting and guided infiltration into the tumor mass[8,11]. However, the underlying strategies differ markedly between central nervous system (CNS) tumors and peripheral solid tumors (such as lung and pancreatic cancers) owing to their distinct anatomical contexts.

In CNS tumors, such as gliomas, nerve recruitment and integration occur within pre-existing neuronal networks. Neurotrophic factors released by

tumor and stromal cells activate Trk receptors on adjacent neurons, promoting fiber sprouting and survival[12,13]. This process is further reinforced by functional synaptogenesis, in which excitatory synapses mediated by AMPA receptors form directly between neurons and glioma cells, transmitting depolarizing currents that sustain intracellular calcium signaling and activate proliferation pathways (CREB and mTOR). In addition, metabolic symbiosis arises, whereby glycolytic tumor cells supply lactate as an energy substrate for the neurons. Collectively, NGF/BDNF-mediated recruitment, AMPA receptor-dependent synaptic integration, and metabolic coupling create a coordinated neurotrophic-synaptic-metabolic triad that embeds the tumor deeply within the host neural circuit[14,15].

In contrast, peripheral solid tumors lack an intrinsic neuronal network and must recruit nerves de novo from the surrounding peripheral nervous system (PNS). Although NGF and BDNF continue to attract sympathetic, sensory, and cholinergic fibers[16], these tumors also depend on axon guidance molecules (e.g., Netrin-1 and SLIT2) to direct nerve ingrowth. Schwann cells should also be considered key contributors to this process, as they act as both sources and responders to neurotrophic signals. Through paracrine communication with cancer cells and nerves, Schwann cells can amplify tumor innervation and establish a microenvironment that supports invasion and tumor progression. A hallmark mechanism of this invasion is PNI, in which cancer cells migrate along the nerve sheaths after remodeling the extracellular matrix to enhance adhesion and establish structural pathways for invasion and dissemination[17]. Thus, peripheral tumors assemble their neuralized niche primarily through chemoattraction, coupled with matrix co-option and invasive tumor progression.

2.2 Neural Signaling in Central Nervous System Tumors

Neural innervation within CNS tumors is unique because it primarily involves the integration and remodeling of the brain's intrinsic neural circuitry rather than infiltration from the PNS. The dominant neural components are local

glutamatergic and GABAergic neurons, which engage in direct bidirectional communication with tumor cells, profoundly influencing tumor progression[15,18-21].

The most distinctive mechanism is the formation of functional excitatory synapses between neurons and tumor cells. In gliomas, cancer cells express AMPA-type glutamate receptors (AMPAR), enabling them to receive direct glutamatergic input from active neurons. Synaptic transmission induces depolarizing currents and activity-dependent calcium influx in tumor cells, activating downstream oncogenic pathways and driving proliferation and invasion. Recent high-impact studies have established that neuron–tumor contacts are bona fide functional synapses rather than passive juxtapositions, thereby reframing tumor innervation as a form of electrochemical integration into host neural circuits. Beyond classical chemical synapses, tumor cells are interconnected via gap junctions (often through tumor microtubes), forming an electrical syncytium that amplifies and synchronizes neuron-derived depolarizing signals across the tumor network. This interconnected network can generate intrinsic rhythmic activities, such as synchronized calcium oscillations or slow membrane potential fluctuations, which coordinate collective tumor cell behaviors and promote growth by enhancing proliferative signaling and invasive capacity[22].

This interaction is reciprocal in nature. Tumor cells actively remodel their neural environment by secreting synaptogenic factors, such as neuroligin-3 (NLGN3) and thrombospondin-1 (TSP-1), which promote the formation of new excitatory synapses in neurons. These findings reflect a broader process of tumor-induced neuronal plasticity, in which malignant cells do not merely respond to pre-existing neural activity but actively reshape neuronal identity, excitability, and circuit architecture to create a more tumor-permissive niche. This leads to neuronal hyperexcitability and circuit rearrangements, creating a feed-forward loop in which increased neuronal activity drives tumor growth, enhancing excitatory signaling and further strengthening the neuron–tumor connection[23]. While this loop highlights the dominant role of excitatory

signals in promoting malignancy, inhibitory signals, particularly GABAergic inputs, can exert context-dependent suppressive effects. However, in advanced stages, tumors may co-opt even inhibitory pathways to support their survival and adaptation to the microenvironment.

Regarding specific neural types, the detailed functional segregation of sympathetic or parasympathetic nerves observed in peripheral tumors is far less well defined in the CNS. Instead, the balance between excitatory (glutamatergic) and inhibitory (GABAergic) signaling is critical for the maintenance of homeostasis. Current evidence indicates that excitatory drive predominates in promoting glioma growth via AMPA/NMDA receptor-mediated calcium influx and downstream oncogenic activation. In contrast, inhibitory GABAergic signaling may serve a context-dependent tumor-suppressive function (e.g., GABAA receptor activation reduces proliferation in hemispheric high-grade gliomas), although its role remains poorly understood and may be altered or exploited during disease progression (e.g., in H3K27M-DMG, altered chloride homeostasis renders GABA depolarizing and growth-promoting)[16].

2.3 Neural Recruitment and Innervation in Peripheral Tumors

In contrast to CNS tumors, peripheral solid tumors (e.g., lung, pancreas, prostate, and stomach cancers) acquire innervation through active recruitment and ingrowth of nerves from the surrounding PNS. This process, often termed tumor-induced axonogenesis or neurogenesis, is a hallmark of cancer progression and is generally associated with poor prognosis[24,25]. The core mechanism involves the secretion of neurotrophic factors by the tumor. NGF, BDNF, and other factors are produced by cancer cells, stromal cells, and infiltrating immune cells within the TME. In addition to NGF and BDNF, peripheral tumors may also release CCL2, CXCL12, IL-6, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5), which further promote neurite outgrowth and reinforce the recruitment of peripheral nerve fibers into the TME. These factors bind to Trk receptors (e.g., TrkA and TrkB) on the termini of nearby

nerves, activating signaling pathways that stimulate neuronal survival and induce directional outgrowth (chemotaxis) of nerve fibers into the tumor mass[26]. This establishes a "neuralized" niche that supports the tumor development. Schwann cells likely contribute to the formation of this niche by participating in bidirectional paracrine signaling with tumor cells and recruited nerves, thereby strengthening tumor-associated innervation and promoting a pro-tumorigenic microenvironment. PNI serves as a distinct route for local metastasis and is a strong negative prognostic indicator, particularly in pancreatic and prostate cancers[27] (**Figure 1**-**2**).

2.4 Tumor-Type Specificity of Peripheral Innervation

Although the core principles of neurotrophic factor secretion and PNI are broadly shared, the composition and functional output of peripheral innervation vary substantially across tumor types, underscoring the need for context-specific therapeutic strategies when targeting the neuro-oncological axis.

Beyond the tumor types discussed below, recent studies have also extended the relevance of peripheral neural regulation to additional malignancies, including breast cancer, small cell lung cancer, and colorectal cancer, further underscoring that neural innervation is a broadly conserved but context-dependent feature of tumor progression.

2.4.1 Pancreatic Cancer

The sympathetic nervous system exerts a dominant tumor-promoting effect in this malignancy, in which norepinephrine (NE) released from sympathetic fibers activates β2-adrenergic receptors (ADRB2) on cancer cells, thereby stimulating their proliferation, angiogenesis, and metastasis[28]. This tumor-promoting effect is reinforced by a β2-adrenergic–neurotrophin feed-forward loop, in which catecholamine-driven ADRB2 signaling increases neurotrophin expression, enhances nerve density, and further amplifies local NE

accumulation, thereby accelerating PDAC progression[29]. Notably, parasympathetic cholinergic signaling via the vagus nerve demonstrates inhibitory activity, as evidenced by preclinical models that retard tumorigenesis. In addition to autonomic innervation, sensory neurons contribute to pancreatic tumor initiation and progression, as their ablation suppresses neurogenic inflammation, delays PanIN formation, and prolongs survival in genetic models of PDAC[30].

Recent single-neuron profiling has further indicated that PDAC reprograms both sympathetic and sensory neurons into tumor-supportive states, establishing a neuron–cancer–microenvironment interactome that may be therapeutically exploitable[31].

At the precursor lesion stage, neuroligin-related programs may also influence pancreatic epithelial progression, as loss of NLGN2 has been linked to the disruption of epithelial polarity and enhanced YAP activity during the transition from low- to high-grade PanIN[32].

2.4.2 Prostate Cancer

This malignancy exhibits a stage-dependent shift in autonomic neural regulation, wherein sympathetic nerves predominantly fuel early carcinogenesis and angiogenesis through sustained adrenergic signaling, whereas parasympathetic nerves assume a prominent role in promoting metastatic dissemination during later phases, thereby illustrating the context-specific and evolving contributions of distinct nerve populations to malignant advancement[33]. In addition, recent evidence indicates that prostate tumors can recruit doublecortin-positive (DCX+) neural progenitors originating from the CNS, which infiltrate primary tumors and metastases, initiate intratumoral neurogenesis, and are associated with a more aggressive disease[34].

2.4.3 Gastric Cancer

This malignancy is marked by synergistic contributions from both the sympathetic and parasympathetic branches of the autonomic nervous system to tumor growth, in which sympathetic signaling through adrenergic receptors (ADRB2) advances disease progression, while parasympathetic acetylcholine engages muscarinic receptors (such as M3) to stimulate the EGFR and Wnt pathways and thereby boost cancer cell proliferation; such interplay underscores the cooperative, rather than opposing, roles of autonomic innervation[35]. Consistently, surgical or pharmacological denervation has been shown to suppress gastric tumorigenesis, inhibit Wnt signaling, reduce stem cell expansion, and enhance the efficacy of systemic chemotherapy, supporting a functional requirement for neural input throughout multiple stages of gastric cancer development[36].

Mechanistically, an ACh–NGF feed-forward loop has been described in the gastric cancer niche, whereby cholinergic stimulation induces NGF expression, expands enteric nerves, and promotes tumorigenesis in an M3R-dependent manner[35].

In addition, acetylcholine can act in an autocrine manner in gastric cancer cells, activating EGFR signaling through M3 receptors to further promote proliferation[37].

2.4.4 Colorectal Cancer

In colorectal cancer, reciprocal crosstalk between sympathetic nerves and cancer-associated fibroblasts establishes a β2-adrenergic–NGF feed-forward loop that promotes tumor progression[28]. This interaction sustains chronic adrenergic signaling, which in turn drives cancer-associated fibroblast activation and secretion of growth factors that support tumor cell survival and invasion. In addition to these local sympathetic nerve–CAF interactions, colorectal cancer cells have been reported to hijack a stress-sensitive brain–gut polysynaptic circuit linking the lateral septum to enteric cholinergic

neurons[38], illustrating that peripheral tumor innervation may also be embedded within higher-order neural circuitry.

2.4.5 Breast Cancer

In breast cancer, sympathetic activation induces a metastatic switch via β-adrenergic signaling and macrophage recruitment[39]. Chronic β-adrenergic stimulation upregulates MMPs and VEGF in the primary tumor, remodeling the extracellular matrix and attracting immunosuppressive macrophages that further promote metastatic dissemination.

2.4.6 Small Cell Lung Cancer

In small cell lung cancer, both peripheral innervation and activity-dependent neuron–tumor interactions have recently been implicated in tumor growth and progression, including synaptic integration in the brain metastatic setting[40,41].

3. Tumors Hijack Neurons to Reprogram Immune Microenvironment

3.1 Sympathetic Signaling as a Central Organizer of Neural Immunosuppression

A central theme emerging from recent studies is that neural regulation of the TME is inseparable from immune suppression, with sympathetic signaling serving as one of its principal organizing axes. Tumor-infiltrating nerves were not isolated. They commonly represent direct extensions of the autonomic nervous system. Within the TME, local sympathetic fibers derived from systemic innervation or newly recruited nerves become integrated and activated. These fibers release NE in response to tumor-derived cues, inflammatory mediators, and systemic stress. NE release follows the canonical process of neurosecretion, in which action potential–driven

depolarization induces calcium influx and vesicular exocytosis into the synaptic cleft or surrounding pericellular space[42-44].

Once released, NE acts as a major immunosuppressive mediator. Through β-adrenergic signaling, it supports the establishment of a stable immunosuppressive TME. Clinical analyses and animal studies have identified this pathway as a major driver of tumor-immune evasion[45]. At the mechanistic level, NE binds to β2-adrenergic receptors (ADRB2) on tumor and stromal cells, activating the PKA/STAT3 axis and promoting the recruitment and activation of myeloid-derived suppressor cells (MDSCs). Adrenergic signaling also directly affects the T-cell fate. β-adrenergic receptors expressed on exhausted or dysfunctional $CD8^+$ T cells suppress cytokine production and proliferation, thereby reinforcing terminal exhaustion. Therefore, sympathetic signaling converges on two complementary routes: tumor/stromal ADRB2–STAT3 signaling and direct immune cell adrenergic responsiveness to NE. STAT3, in turn, induces chemokines such as CCL2 and CXCL-family mediators, further supporting the recruitment of MDSC subsets[46].

NE also stimulates the production of cytokines, including IL-6 and VEGF, creating a niche that supports MDSC expansion, survival, and functional activation in the TME. Because MDSCs express adrenergic receptors, they can respond to NE and amplify this suppressive circuitry through positive feedback loops. The downstream effect is a broader weakening of antitumor immunity, characterized by reduced $CD8^+$ T-cell proliferation and effector function. However, nerve-associated immune suppression is not limited to adrenergic signaling. Cancer-induced nerve injury can trigger a chronic inflammatory repair program within tumor-associated nerves, characterized by IL-6- and type I interferon-mediated signaling, which progressively shifts the TME toward an exhausted and suppressive state. This mechanism links nerve injury to $CD8^+$ T-cell dysfunction and resistance to anti-PD-1 therapy[47]. Sympathetic input also directly regulates $CD8^+$ T-cell fate. Exhausted $CD8^+$ T cells upregulate β1-adrenergic receptors (ADRB1), and catecholamine

exposure suppresses their proliferation and cytokine production while promoting progression toward terminal exhaustion. These cells also cluster around sympathetic nerves in an ADRB1-dependent manner, providing direct evidence that tissue innervation shapes T-cell exhaustion within the TME[48]. The effects of sympathetic signaling extend beyond the terminal exhaustion. In barrier tissues, such as the skin, NE-ADRB2 signaling acts indirectly through keratinocytes, modulating epithelial CXCL16-dependent cues that govern the recruitment and positioning of $CD8^+$ tissue-resident memory T cells, thereby tuning local cancer immunosurveillance[49].

Macrophage biology is also influenced by NE. In prostate cancer models, sympathetic signaling drives tumor-associated macrophages (TAMs) toward an M2-like phenotype. The tumor–brain axis described in lung adenocarcinoma reinforces the immune significance of this pathway, showing that vagal sensory input can increase sympathetic output within the TME and suppress antitumor immunity through β2-adrenergic signaling in alveolar macrophages. These polarized TAMs release immunosuppressive cytokines, such as IL-6 and TGF-β, thereby strengthening the suppressive network[50]. TAMs are not simply passive neural cue recipients. Recent studies have indicated that they actively regulate tumor innervation. Beyond their immunosuppressive functions, TAMs display a neural growth gene signature and can directly promote intratumoral nerve infiltration and neurite outgrowth through mediators such as secreted phosphoprotein 1 (SPP1), linking macrophage activity to both neural remodeling and tumor progression[51].

In prostate cancer models, ADRB2 signaling is strongly correlated with high levels of MDSC infiltration. β-blockers or specific ADRB2 antagonists can reduce MDSC accumulation, restore T cell activity, and improve the efficacy of PD-1/PD-L1 immune checkpoint blockade therapy[52]. Taken together, these observations indicate that sympathetic nerves act within the TME as a central organizer of immune evasion by establishing a neural–MDSC–T cell

suppression axis. This axis represents a plausible therapeutic target for overcoming resistance to immunotherapy (**Figure 3**).

3.2 Parasympathetic Regulation and the Cholinergic Anti-inflammatory Pathway

The parasympathetic nervous system participates in tumor immune regulation through acetylcholine (ACh)-mediated cholinergic anti-inflammatory pathways; however, its effects exhibit significant tissue specificity and complexity[53]. On one hand, ACh activates α7 nicotinic acetylcholine receptors (α7nAChR) on macrophage surfaces, inducing M2 polarization and secretion of anti-inflammatory factors such as IL-10 and TGF-β, while inhibiting dendritic cell maturation and T cell responses, thereby creating an immunosuppressive microenvironment. This effect has been demonstrated in various solid tumors and represents one of the key mechanisms underlying parasympathetic neurotropic effects on cancer. However, a seemingly paradoxical phenomenon has been observed in pancreatic cancer: the parasympathetic nervous system inhibits tumor cell proliferation via muscarinic receptors (CHRM1), exerting certain anticancer effects while simultaneously enhancing the immunosuppressive properties of macrophages[54], suggesting functional decoupling between tumor growth regulation and immune responses. This "dual role" highlights the complexity of cholinergic signaling in tumor immunity, indicating that clinical interventions require precise evaluation based on specific tumor types and microenvironmental contexts. Mechanistically, cholinergic signaling appears to be receptor- and cell-type-dependent. α7nAChR signaling predominantly shapes macrophage polarization and anti-inflammatory cytokine production, whereas muscarinic signaling through CHRM1 may exert distinct effects on epithelial tumor cells and immune compartments. This receptor-level divergence may underlie the context-specific outcomes of parasympathetic regulation in different tumor types.

3.3 Sensory-Neural Regulation of Tumor Immunity

Sensory nerves exert precise modulation of tumor immunity through the release of neuropeptides, with CGRP and substance P (SP) serving as core mediators that perform bidirectional immunomodulatory functions[28]. By binding to its receptor complex RAMP1/CLR, CGRP directly inhibits the activation, proliferation, and cytotoxicity of $CD8^+$ T cells while promoting the expansion of regulatory T cells (Treg), thereby establishing an immunotolerant microenvironment[28]. Recent work has further extended this mechanism by identifying an epigenetic checkpoint downstream of the CGRP-RAMP1 neuroimmune axis, whereby neuroimmune signaling promotes $CD8^+$ T-cell exhaustion and remodels chromatin accessibility at loci associated with effector differentiation and exhaustion[55]. In head and neck cancer and oral squamous cell carcinoma, sensory nerves release CGRP, which interferes with TCR signaling via the cAMP-PKA pathway, "paralyzing" the antitumor function of T cells at the molecular level. This establishes a direct neuropeptide-mediated functional interaction between sensory nerves and adaptive immune cells, in which CGRP signaling shifts the balance from cytotoxic antitumor immunity toward immune tolerance. In parallel, substance P may further modulate inflammatory cell behavior in a context-dependent manner, linking sensory innervation to both immune suppression and tumor-associated inflammation. Targeting the CGRP signaling pathway (e.g., using CGRP receptor antagonists) may represent a novel strategy to reverse immunosuppression and restore T cell activity[28]. CGRP receptor antagonists increased $CD8^+$ T cell infiltration by 2.3-fold in oral squamous cell carcinoma mouse models. Additionally, SP can enhance inflammatory responses under specific conditions but predominantly promotes immunosuppression. This neuropeptide-mediated immunomodulation reveals the dual role of sensory nerves as both "immune sentinels" and "immunosuppressors," with their net effect depending on the tumor type, neural density, and local signal concentration.

3.4 Structural and Spatial Basis of Neuro-Immune Crosstalk

Neural–immune communication depends on more than soluble mediators. It is also sustained by structural contacts and spatial proximity, together forming a functional unit often referred to as the “neuroimmune synapse.” Research on both intracranial and extracranial tumors has strengthened the view that neural regulation of immunity is not incidental to tumor progression but is a fundamental feature of tumor ecology, operating through spatially organized and functionally active neuro-immune interfaces. Electron microscopy studies of head and neck cancer models have revealed synapse-like structures between sensory nerve terminals and $CD8^+$ T cells. These interfaces permit polarized CGRP-RAMP1 signaling and directly suppress T cell function[56,57]. A complementary line of evidence points to a reverse-feedback, neuroimmune mechanism. Cancer cells can injure tumor-associated nerves through myelin degradation, and the injured nerves initiate an IL-6- and type I interferon-mediated repair program. As this injury accumulates, the regenerative response becomes chronic and drives an exhausted, suppressive immune state associated with resistance to anti-PD-1 therapy[47]. The implications are clear: spatially organized nerve–immune interfaces are not merely anatomical associations. They function as signaling units that constrain cytotoxic immune surveillance in the TME.

Tumors can also adopt CNS-like metabolic programs to disrupt immune cell communication. Recent studies have shown that the CNS-enriched metabolite N-acetylaspartate (NAA), produced through NAT8L, impairs immunological synapse formation in natural killer (NK) cells and $CD8^+$ T cells, thereby weakening cytotoxic function and promoting immune evasion. This finding reinforces the broader concept that tumors co-opt neural regulatory programs to suppress antitumor immunity[58] (**Figure 4**).

Tumor-derived exosomes add another layer to this phenomenon. p53-deficient tumor cells release exosomes containing miR-34a, which are taken

up by neurons and induce NGF secretion, thereby promoting immunosuppressive neural remodeling. Exosomes carrying miR-21/324 can also drive macrophage polarization toward the M2 state by targeting SOX9 and PTEN, establishing a tumor–exosome–neuro–immune regulatory cascade[59,60].

3.5 Neural Establishment of an Immunosuppressive Microenvironment

The polarization of TAMs represents another pivotal mechanism. Nerve-epithelial cells (NEs) drive TAMs toward M2 polarization via the ADRB2 signaling pathway. Recent work has further refined this mechanism by showing that cancer cells can co-opt an inter-organ neuroimmune circuit in which nociceptive-neuron activation and CGRP release remodel tumor-draining lymph nodes into an immune-suppressed state. In this context, reduced CCL5 secretion promotes M2-like polarization of TAMs, thereby facilitating tumor growth and diminishing immune checkpoint blockade efficacy. These macrophages secrete anti-inflammatory factors, such as IL-10 and TGF-β, which suppress dendritic cell maturation and T-cell responses, thereby enhancing immune tolerance[61]. In pancreatic cancer, neuroinflammatory responses promote the recruitment of monocytes from peripheral blood to the TME through the CCL2-CCR2 chemokine axis, where they differentiate into M2 macrophages, further amplifying the immunosuppressive effects. This neuro-macrophage interaction forms a positive feedback loop that continuously consolidates the immunosuppressive microenvironment. Importantly, this macrophage-centered circuit likely extends beyond the conventional M1/M2 framework. Recent studies have indicated that TAMs can adopt a neural growth-supporting phenotype characterized by genes associated with axon regeneration, synapse-related programs, and tissue repair, enabling them to promote both tumor innervation and neural regenerative responses. This expanded view suggests that macrophages contribute not only to immune suppression but also to the

structural and functional remodeling of the neural tumor niche[51].

Taken together, these multifaceted neural–immune interactions underscore the complex spatial and functional organization of neuro-immune crosstalk within the TME. Collectively, they demonstrate that tumors employ a sophisticated strategy of “neuron hijack” by recruiting and reprogramming sympathetic, parasympathetic, and sensory circuits through neurotrophic factors and bidirectional signaling. In this manner, cancer cells hijack neural cues to simultaneously promote proliferation, metabolic reprogramming, and immunosuppression, with the tripartite neuro-immune-tumor circuit serving as the primary manifestation of this process. As a result, the nervous system is co-opted from a physiological host regulator into a self-reinforcing, tumor-supportive niche across both CNS and peripheral malignancies.

4. Tumors Hijack Neurons to Disrupt the Endocrine System

Building on the above local neuroimmune mechanisms, neural control of tumor progression also engages systemic neuroendocrine circuits to remodel host endocrine signaling. Beyond intratumoral neuroimmune crosstalk, autonomic innervation exerts potent systemic effects via the neuroendocrine axis: neural signals directly modulate endocrine hormone secretion, thereby reprogramming tumor metabolism and progression independent of immune regulation. Sympathetic hyperactivity, frequently amplified by chronic stress, serves as the primary physiological driver of neuroendocrine dysregulation, activating efferent pathways that trigger sustained hormonal release and establish a self-amplifying feed-forward loop that further accelerates tumor progression[62-64].

4.1 Systemic Hormonal Signaling: The Neuroendocrine Cascade

Autonomic innervation plays a central role in orchestrating systemic hormone release, which reprograms tumor metabolism and proliferation, independent of local immune intermediates. Sympathetic hyperactivity, frequently

amplified by chronic stress, activates preganglionic fibers projecting to the adrenal medulla, thereby triggering catecholamine (epinephrine and norepinephrine) secretion in the adrenal medulla. These catecholamines engage β-adrenergic receptors on distant tumor cells, elevating intracellular cAMP/PKA and ERK/MAPK cascades to enhance glycolysis and cell cycle progression[65]. The same sympathetic outflow concurrently stimulates the hypothalamic–pituitary–adrenal axis, promoting adrenocortical glucocorticoid (cortisol) release, whose binding to tumor glucocorticoid receptors represses p53-mediated apoptosis while upregulating VEGF and gluconeogenic enzymes, thereby sustaining malignant expansion even under nutrient limitation[66]. Together, these pathways illustrate how systemic neural signaling enhances tumor metabolic plasticity, enabling malignant cells to adapt to fluctuating nutrient and oxygen availabilities while maintaining proliferative fitness. Remarkably, beyond classical neuropeptide secretion, cancer-associated neurons can also directly transfer intact mitochondria to adjacent cancer cells through tunneling nanotubes or direct intercellular contacts, a process that markedly enhances tumor bioenergetics and metastatic fitness[67].

4.2 Direct Neurosecretory Effects: Neurons as Endocrine Cells

Tumor-infiltrating nerves can function as endocrine effectors by releasing neuropeptides that act beyond the local microenvironment and exert systemic effects on neoplastic cells. Sensory and autonomic fibers secrete CGRP and substance P, which bind to cognate receptors on tumor cells, alter intracellular calcium dynamics, and activate anabolic pathways, such as mTOR, thereby promoting proliferation and metabolic reprogramming without intermediary stromal involvement[68]. Cholinergic neurons can also release acetylcholine that reaches distant sites through circulation, attenuating insulin-like growth factor signaling and restraining tumor anabolic demand[69]. Taken together, these observations define a direct neuropeptide-to-tumor signaling axis in which neuron-derived mediators

reshape intracellular calcium handling and growth-related metabolic pathways.

4.3 Neuropeptides as Endocrine Modulators: Beyond Local Action

Neuropeptides originating from tumor-associated nerves extend their influence systemically as endocrine modulators, transcending local paracrine effects to reshape hormonal homeostasis at distant sites. Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP), released by autonomic fibers, circulate to influence hypothalamic and pituitary output, indirectly modulating growth hormone and thyroid hormone levels, which in turn reprogram tumor cell metabolism via cAMP-dependent transcription[70]. Substance P exerts endocrine-like actions by stimulating adrenal steroidogenesis and amplifying glucocorticoid surges that sustain tumor energy demands[71]. Collectively, these mechanisms underscore the neuroendocrine axis as a multilayered regulator whose molecular vulnerabilities, independent of immune mediation, warrant targeted interventions, such as receptor antagonists or nerve-modulating agents, to complement existing neuro-oncology strategies[72].

5. Tumors Hijack Neurons to Reprogram Metabolic Plasticity

Tumors hijack neural regulation of host metabolism at both systemic and cellular levels to enhance their metabolic adaptability and support tumor progression under stressful conditions[73].

5.1 Adipose Tissue-Neural Interactions: Neuro-Adipokines as Metabolic Bridges

Neural regulation of adipose tissue generates neuro-adipokines that serve as endocrine bridges between innervation and tumor progression in the TME. Sympathetic fibers innervating white and brown adipose depots modulate lipolysis, thermogenesis, and adipokine secretion in a depot-specific manner.

In white adipose tissue (WAT), sympathetic activation promotes lipolysis and elevates circulating leptin levels, which engage Ob-R receptors on tumor cells to activate the JAK/STAT and PI3K/AKT pathways, thereby enhancing tumor cell survival and metastatic potential[74]. In brown adipose tissue (BAT), sympathetic stimulation via β3-adrenergic receptors drives thermogenesis and "browning" of WAT, leading to increased energy expenditure that contributes to cancer cachexia while releasing adipokines such as adiponectin and FGF21, which exert context-dependent effects on tumor metabolic reprogramming[75].

Conversely, parasympathetic tone can help restore adiponectin release, whose binding to AdipoR1/R2 receptors on neoplastic cells suppresses mTOR activity and lipid synthesis. These findings indicate that neural control of adipose tissue can indirectly reprogram tumor metabolism by altering the systemic availability of adipokines and energy substrates, thereby linking the host metabolic state to malignant progression.

5.2 Direct Neural-to-Cancer Mitochondrial Transfer: Enhancing Tumor Metabolic Plasticity

In parallel, tumors establish direct physical interactions with cancer-associated neurons to hijack functional mitochondria. Cancer-associated neurons undergo metabolic reprogramming, resulting in increased mitochondrial mass, and subsequently transfer intact mitochondria to adjacent cancer cells through tunneling nanotubes or direct intercellular contacts formed along tumor-innervating nerves.

Using breast cancer denervation models and co-culture systems, these neurons significantly boost oxidative phosphorylation (OXPHOS) capacity, ATP production, and overall metabolic plasticity in the recipient cancer cells. To track this process, the study developed MitoTRACER, a genetic reporter

that permanently labels recipient cancer cells and their progeny upon mitochondrial acquisition.

Lineage tracing further revealed that cancer cells receiving neuronal mitochondria in the primary tumor are selectively enriched at metastatic sites following dissemination. This transfer confers critical advantages for surviving nutrient deprivation, oxidative stress, and the demanding conditions of the metastatic niche, thereby promoting invasion, colonization, and resistance to therapy. The process is tightly coupled to tumor-induced neural remodeling and PNI, exemplifying tumor neuron hijack at the organelle level[67].

6. Tumors Hijack Neurons to Induce Cancer-associated Pain

Cancer-associated pain, most commonly arising from PNI and direct nerve infiltration by tumor cells, extends far beyond a symptomatic consequence to become an active participant in neuroendocrine dysregulation[76]. Persistent nociceptive signaling from tumor-infiltrating sensory fibers triggers central sensitization within the spinal dorsal horn and higher brain centers, thereby amplifying efferent sympathetic outflow and reinforcing autonomic hyperactivity[77]. This heightened sympathetic tone feeds directly into the hypothalamic–pituitary–adrenal axis, escalating catecholamine and glucocorticoid release, which, in turn, further stimulates tumor metabolism and proliferation through the same β-adrenergic and glucocorticoid receptor pathways described earlier. Concurrently, pain-induced nerve hyperactivity augments the secretion of neuropeptides, such as substance P and CGRP, from both sensory and autonomic fibers, converting localized nociceptive input into a systemic endocrine signal that sustains a self-reinforcing circuit of hormonal reprogramming, independent of immune intermediates[78]. The resulting vicious cycle, wherein pain severity correlates with accelerated tumor progression and poorer clinical outcomes, highlights the neuroendocrine axis as a therapeutically actionable vulnerability, which may

be disrupted by targeted neuromodulatory agents or receptor antagonists to interrupt both symptomatic burden and malignant drive[79].

7. Tumors Hijack Neurons to Reshape the Host Macroenvironment and Tumor Niche

In addition to the local neural and neuroendocrine mechanisms described above, nerves influence cancer progression by coordinating host-wide physiological states (macroenvironment) and directly remodeling the tumor microenvironment (TME, also referred to as the tumor niche). The nervous system exerts a profound and multifaceted influence on cancer progression, operating across two interconnected scales: the systemic, organism-wide macroenvironment and the local tumor niche (TME). This dual regulation integrates the tumor into the host's physiology while simultaneously constructing a supportive niche for its growth and spread.

7.1 Systemic Regulation: Orchestrating the Host Macroenvironment

At the systemic level, the nervous system, particularly its autonomic branches, shapes the physiological state that makes the host environment more or less permissive for cancer progression.

The sympathetic nervous system (SNS) serves as a critical link between psychological stress, physiological responses, and cancer outcomes. Under chronic stress, sustained SNS activation stimulates the hypothalamic–pituitary–adrenal (HPA) axis, leading to the systemic release of catecholamines (e.g., norepinephrine) and glucocorticoids (e.g., cortisol). This hormonal milieu induces systemic immunosuppression by inhibiting the function of NK cells and cytotoxic T lymphocytes while promoting a proinflammatory cytokine profile. This creates a "fertile soil" that facilitates tumor seeding, growth, and distant metastasis[54]. Mechanistically, this neuroendocrine state links sympathetic activation to immune dysfunction by reducing cytotoxic lymphocyte competence, while simultaneously promoting

inflammatory and stromal conditions that favor metastatic outgrowth. Conversely, the parasympathetic nervous system (PNS), primarily via the vagus nerve, generally exerts a counterbalancing anti-inflammatory effect through the cholinergic anti-inflammatory pathway, although its systemic role in cancer remains complex and context-dependent[61].

The SNS also plays a key role in the regulation of whole-body energy homeostasis. Through the release of catecholamines such as NE, the SNS stimulates lipolysis in adipose tissue and glycogenolysis in the liver, thereby mobilizing energy substrates, including free fatty acids and glucose, into the circulation. Tumors, which often exhibit heightened glycolytic metabolism known as the Warburg effect, can exploit this SNS-driven systemic metabolic shift by utilizing the increased availability of glucose and free fatty acids to satisfy their elevated anabolic and bioenergetic demands[54]. Thus, neural activity not only increases substrate availability but may also enhance tumor metabolic plasticity, allowing cancer cells to flexibly adapt their bioenergetic programs during growth and dissemination. In this way, neural activity can indirectly fuel tumor progression by reprogramming host metabolism to create a nutrient-rich milieu that supports rapid cancer growth and proliferation[52].

In addition to mobilizing peripheral energy substrates, tumor-associated neuroimmune signaling may disrupt the central mechanisms of energy homeostasis and behavior. Recent studies have identified a cytokine-sensing brainstem-to-basal ganglia circuit that detects elevated IL-6 levels during cancer cachexia and translates systemic inflammation into apathy-like behavioral changes through reduced mesolimbic dopamine signaling. More broadly, cancer cachexia has been framed as a tumor-driven disruption of whole-body homeostasis involving coordinated immune, metabolic, endocrine, and neural networks, suggesting that tumor-associated neuroimmune signaling can extend beyond local tumor-promoting effects to centrally and

systemically regulate host physiology[80,81].

7.2 Local Regulation: Direct Remodeling of the Tumor Microenvironment

Within the TME, nerves engage in direct, paracrine, and electrochemical communication with both tumor and stromal cells to promote malignancy.

Direct Control of Tumor Cell Behavior: Nerve-derived signals directly activate oncogenic pathways in cancer cells. As detailed in the previous sections, neurotransmitters such as NE bind to β2-adrenergic receptors (ADRB2) and activate downstream signaling cascades, including the cAMP/PKA and PI3K/AKT pathways. Importantly, the functional output of these pathways depends on the target cell type; in tumor cells, they enhance proliferation and survival, whereas in stromal compartments, such as endothelial cells and fibroblasts, they promote angiogenesis, matrix remodeling, and niche support. These pathways operate primarily in tumor cells and are also active in key stromal components, such as endothelial cells (promoting angiogenesis) and cancer-associated fibroblasts (facilitating matrix remodeling). Collectively, their activation enhances tumor cell proliferation, invasion, and resistance to apoptosis[54,56].

Acetylcholine signaling through muscarinic receptors (e.g., M3R) can activate the EGFR and Wnt/β-catenin pathways to drive tumor cell proliferation and stemness, particularly in gastrointestinal cancers[57,61]. Glutamate released from neurons forms AMPA receptor-mediated synapses with glioma cells, leading to activity-dependent calcium influx and activation of the CREB and mTOR pathways, which drive growth[82]. These examples illustrate that the neural regulation of tumor behavior is mediated through receptor-defined signaling modules, including adrenergic, muscarinic, and glutamatergic pathways, which converge on core proliferative and metabolic effectors. Remodeling of the Stromal and Vascular Niche: Nerves Critically Shape the Non-Cellular Components of the TME. SNS-derived NE can

stimulate the production of vascular endothelial growth factor (VEGF) from both tumor and stromal cells, promoting angiogenesis to supply nutrients and oxygen[54]. This establishes a direct mechanistic link between adrenergic signaling and vascular remodeling, whereby neural input stimulates pro-angiogenic factor production and reshapes endothelial behavior within the tumor niche. Furthermore, nerves release factors such as netrin-1 and SLIT2, which guide axons and influence the behavior of cancer-associated fibroblasts and endothelial cells, facilitating matrix remodeling and creating paths for invasion[28,83].

This concept is further supported by studies showing that class 3 semaphorins regulate vascular morphogenesis by modulating endothelial integrin function, thereby linking canonical axon-guidance programs to endothelial adhesion, migration, and vascular remodeling[84].

Consistently, Slit-Robo signaling has been reported to promote endothelial cell recruitment and tube formation, and the blockade of Robo activity reduces microvessel density and tumor growth in vivo, further supporting a direct role for neural guidance cues in tumor angiogenesis[85]. In addition, semaphorin family members beyond class 3 semaphorins can exert pro-angiogenic functions. For example, Sema4D has been shown to stimulate endothelial migration and capillary-like tube formation through its high-affinity receptor Plexin B1, with these angiogenic effects requiring coupling to the Met tyrosine kinase pathway[86].

8. Tumors Hijack Neurons to Drive Tumor Angiogenesis, Invasion, Metastasis and Progression.

Neural activity not only regulates immunity but also indirectly drives tumor angiogenesis and invasion/metastasis through metabolic reprogramming and signaling regulation, thereby promoting tumor progression. The prostate cancer study first revealed this synergistic mechanism[87].

In terms of angiogenesis, neurotransmitters directly participate in the process of neovascularization. For example, NE upregulates the expression of vascular endothelial growth factor (VEGF) in tumor and stromal cells via the ADRB2 receptor, promoting endothelial cell proliferation and angiogenesis[54]. In addition to neurotransmitter-driven VEGF signaling, axon-guidance molecules exert important regulatory effects on tumor angiogenesis. Semaphorin 3A (Sema3A), for example, has been shown to improve tumor oxygenation, extend the vascular normalization window, and suppress hypoxia-driven invasion and metastatic dissemination, highlighting the functional overlap between neural guidance programs and angiogenic remodeling[88].

In prostate cancer models, ADRB2 signaling further activates the PI3K-AKT pathway in endothelial cells, enhancing angiogenic capacity and inhibiting oxidative phosphorylation metabolism, thereby promoting the transition of endothelial cells to glycolytic metabolism to adapt to the hypoxic microenvironment[89]. Simultaneously, the sympathetic nervous system enhances glycolytic activity in endothelial cells by regulating metabolic reprogramming, providing energy and biosynthetic precursors to support rapid neovascularization. Activation of this "neuro-metabolic-vascular" axis provides the structural and nutritional foundation for rapid tumor growth and distant metastasis. Mechanistically, neural signaling couples endothelial metabolic adaptation, proangiogenic factor induction, and stromal remodeling, thereby linking neurotransmitter input to vascular expansion and metastatic competence.

PNI is an independent prognostic factor for tumor progression, as it remodels the microenvironment through a multi-cascade mechanism. PNI not only disrupts the stromal barrier surrounding nerves but also provides a "neural fiber highway" for tumor cells, facilitating their spread along plexiform spaces and mediating local invasion[90]. Beyond serving as a physical route for

dissemination, the perineural niche also concentrates neurotrophic and chemotactic signals, thereby functioning as a local signaling hub that integrates invasion, survival, and microenvironmental remodeling processes. In pancreatic cancer, tumor cells and nerves engage in bidirectional chemotaxis via the SLIT2-ROBO1 axis, forming a "tumor-neural co-migration" pattern that significantly enhances the invasive capacity.

Additionally, neurotrophic factors (e.g., NGF) secreted by nerves can activate TRKA-associated signaling in tumor cells and promote invasive behavior, partly through mechanisms linked to epithelial-mesenchymal transition and matrix remodeling[29]. Under chronic stress, sustained sympathetic nerve activity systematically promotes tumor metastasis through the β-adrenergic signaling pathway, further exacerbating disease progression[91].

Thus, neuro-environmental remodeling of the TME is manifested through a cascading amplification effect of "immunosuppression—angiogenesis—invasion and metastasis," forming a self-reinforcing tumor-promoting ecosystem dominated by neural signals. This profoundly influences tumor initiation, progression, and therapy response.

For instance, clinical studies have established PNI and increased intratumoral nerve density as independent poor prognostic indicators in several cancers, including prostate and pancreatic malignancies. Furthermore, retrospective analyses and emerging prospective trials suggest that modulating neural signaling, such as with β-blockers, can influence metastasis and potentially enhance responses to immunotherapy. These clinical observations validate the mechanistic insights discussed, underscore the relevance of the neural niche as a therapeutic target, and provide a translational rationale for developing strategies that disrupt the tumor-nerve axis to improve patient prognosis[92].

9. Therapeutic Implications and Clinical Translation

The mechanistic insights discussed above provide a rationale for translating the neuro-oncology axis into therapeutic strategies, ranging from drug repurposing to combination immunotherapy.

9.1 Repurposing Established Neuroactive Drugs

With the in-depth elucidation of the neuro-oncology interaction mechanism, a group of classical drugs widely used in cardiovascular and neurological fields have demonstrated novel therapeutic value in targeting the neuro-oncology axis, with β-blockers and cholinergic drugs being representative examples[87].

β-blockers are the most extensively studied drug class. These agents function by competitively antagonizing β2-adrenergic receptors (ADRB2) on the surfaces of tumor and stromal cells. By occupying receptor-binding sites, they effectively block the binding of NE released by the sympathetic nervous system. This inhibition prevents the activation of downstream oncogenic signaling cascades, such as PKA/CREB and PI3K/AKT, thereby suppressing tumor proliferation, angiogenesis, and immune evasion[54,91]. Clinical studies have demonstrated that the use of the non-selective β-blocker propranolol in patients with breast cancer reduces lymph node metastasis by 47% and enhances the efficacy of immune checkpoint inhibitors, suggesting its immunomodulatory synergistic effects[93]. Cholinergic agonists also have broad application prospects by modulating parasympathetic signaling and exerting bidirectional regulatory effects on various tumors. Their mechanisms involve the activation of muscarinic receptors (e.g., M1R and M3R), thereby inhibiting the WNT/β-catenin pathway in gastric cancer or promoting the formation of an antitumor immune microenvironment in pancreatic cancer[94,95]. Clinical evidence indicates that M3R antagonists (e.g., darifenacin) can be used to treat gastric cancer, effectively inhibiting tumor growth. In pancreatic cancer models, cholinergic agonists (e.g., bethanechol) can delay the progression of pancreatic intraepithelial neoplasia (PanIN) to

invasive cancer, suggesting their potential for precancerous intervention[96]. These studies provide a solid foundation for the repositioning of cholinergic drugs for tumor prevention and treatment.

Ongoing analgesic drug research and development further expand the repertoire of neuromodulatory agents with dual analgesic and antitumor potential.

9.2 Analgesic Strategies Targeting the Neuro-Oncology Axis

Research on analgesics that specifically target the neuro-oncology axis now focuses on the dual objective of relieving cancer-associated pain while simultaneously disrupting tumor-promoting neural signals. A central emphasis has been placed on the nerve-growth-factor (NGF)/TrkA pathway, a pivotal driver of nociceptor sensitization and PNI. Monoclonal antibodies directed against NGF, such as tanezumab, demonstrated clinically meaningful reductions in pain intensity in a Phase III randomized placebo-controlled trial of patients with bone-metastasis–associated cancer pain. These agents also attenuated tumor-induced nerve sprouting and neuroma formation in preclinical bone cancer models. However, the clinical development of tanezumab was subsequently discontinued[72,97].

Parallel lines of investigation are evaluating calcitonin-gene-related peptide (CGRP) receptor antagonists, which were first approved for migraine, for potential oncology indications. Recent preclinical studies in melanoma and osteosarcoma models have indicated that CGRP blockade (for example, with rimegepant or olcegepant analogs) can reverse $CD8^+$ T-cell exhaustion, lower pain scores, and attenuate both tumor progression and angiogenesis[98,99].

To improve the therapeutic index and overcome delivery barriers, substantial efforts have been directed toward tumor-targeted nanocarrier platforms for analgesic payloads. These systems encompass ligand-functionalized

nanoparticles that incorporate anti-NGF/TrkA antibodies, substance P analogs, or TRPV1 antagonists, which are engineered for high intratumoral accumulation and minimized systemic exposure[100]. Collectively, these developments illustrate how analgesic research is converging with neuro-oncology to bridge symptomatic relief and disease modification, offering a concrete translational bridge from mechanistic insights to bedside applications (**Figure 5**; **Table 2**).

9.3 Combination Strategies with Immunotherapy

Monotherapy often fails to overcome the complex immunosuppressive network of tumors, whereas the combination of neuromodulatory drugs with immunotherapy is emerging as a cutting-edge strategy to enhance therapeutic efficacy[28].

The combination of neuromodulatory drugs and immune checkpoint inhibitors has a strong theoretical foundation. The sympathetic nervous system promotes PD-L1 expression and amplifies regulatory T cells (Tregs) via ADRB2 signaling, whereas cholinergic signaling enhances $CD8^+$ T cell activity and reverses immune exhaustion[56]. Experimental evidence has demonstrated that in breast cancer models, the combination of β-blockers and anti-PD-1 therapy significantly reduces the infiltration of TAMs and MDSCs, while improving the infiltration and function of effector T cells within tumors[96]. In melanoma, blocking CGRP secreted by sensory nerves reverses $CD8^+$ T cell exhaustion and significantly improves the response to immunotherapy. These findings have driven several clinical trials, such as NCT04295759 (an ADAM10 inhibitor targeting NLGN3) and NCT04497142 (an AMPAR antagonist combined with immunotherapy), aimed at exploring the synergistic potential of neural signaling pathways and immunotherapy[28].

The core advantage of this strategy lies in its dual approach: on one hand, it weakens the neuro-mediated immune suppression barrier, and on the other

hand, it activates the T-cell-dominated antitumor immune response, thereby breaking immune tolerance and achieving a more durable therapeutic response[13].

10. Challenges in Clinical Translation

Despite the promising prospects of neuro-targeted therapy, its clinical translation remains challenging and requires multidisciplinary research for advancement. The primary issue lies in the spatiotemporal heterogeneity of neuro-oncological crosstalk. Significant differences exist in neural innervation patterns, receptor expression profiles, and functional effects across different tumor types, stages, and anatomical locations, necessitating context-specific therapeutic strategies[96]. Research in this field faces several concrete technical and methodological hurdles:

10.1 Modelling Complexity in Preclinical Systems

Standard immunodeficient mouse models typically fail to maintain an intact, functional autonomic, and sensory nervous system capable of engaging human tumor xenografts. Although genetically engineered counterparts can preserve more of the host neural circuitry, they still fall short of faithfully reproducing the intricate human-specific neurotumor interactions seen in patients. Real-time, longitudinal visualization of nerve ingrowth, remodeling, and functional dynamics inside a progressively expanding tumor in vivo presents another formidable barrier, one that calls for sophisticated intravital approaches, such as multiphoton microscopy paired with selective neuronal labeling, which remain expensive and inherently low-throughput[101-103].

10.2 Technical Hurdles in Detection and Quantification

Standard histopathological staining, such as hematoxylin and eosin (H&E) staining, frequently underestimates the presence of nerves within tumors. Although immunohistochemistry targeting markers such as PGP9.5, β-III

tubulin, or TH is routinely performed, the lack of standardized protocols limits interpretive reliability, and distinguishing pre-existing nerves from newly sprouted fibers or PNI remains difficult on static tissue sections. Mapping the precise spatial relationships among nerves, immune cells, and cancer cells therefore demands highly multiplexed imaging techniques—exemplified by imaging mass cytometry and CODEX—while deciphering the bidirectional signaling between these compartments requires single-cell or spatial transcriptomics applied to both neuronal and tumor elements, an undertaking rendered particularly challenging by the relative scarcity of neural constituents in most tumor samples[104-107].

10.3 Functional Analysis Bottlenecks

Disentangling whether neural remodeling initiates tumor progression or merely follows as a byproduct continues to defy straightforward resolution. Although optogenetic and chemogenetic strategies are increasingly employed to target discrete nerve populations in preclinical models, they still rely on elaborate experimental setups that constrain their scalability. Compounding this difficulty is the need to capture real-time neurotransmitter concentrations, such as NE and acetylcholine, directly within the TME. Despite their established role, microdialysis probes are invasive and spatially limited[13].

10.4 Clinical and Translational Challenges

Designing clinical trials for neuromodulatory therapies, such as repurposed β-blockers, carries distinctive challenges, including the selection of dosing regimens that diverge from cardiovascular indications, determination of optimal timing across neoadjuvant, concurrent, or maintenance phases, and adoption of endpoints that go beyond standard tumor shrinkage to encompass variations in pain scores, pathological neural density, and immune microenvironment metrics. These challenges are intensified by the absence

of reliable non-invasive biomarkers, such as specific MRI sequences or circulating markers, for quantifying tumor innervation or neural activity in patients, which impedes effective stratification and treatment monitoring. At the foundation of these limitations lies the logistical difficulty of obtaining fresh tumor tissue with intact peritumoral neural architecture for functional studies, as the majority of archival tissues are formalin-fixed and thereby preclude several molecular analyses[28,108,109].

10.5 Addressing Translational Hurdles

To harness the therapeutic potential of neuromodulatory strategies in cancer, several translational hurdles must be overcome. The systemic toxicity of neuroactive agents, exemplified by the cardiovascular liabilities of β-blockers, continues to restrict their clinical deployment. Therefore, future efforts should prioritize tumor-specific delivery platforms, particularly neuro-targeted nanocarriers engineered to concentrate the drug locally while limiting off-target exposure[13].

Preclinical studies have evaluated multiple neuro-targeted nanocarrier platforms. These range from ligand-decorated nanoparticles functionalized with molecules that selectively engage receptors enriched on nerves and tumor-associated neural elements, such as anti-NGF/TrkA antibodies or peptides directed at NGF signaling pathways, and neuropeptide derivatives, such as substance P analogs that bind neurokinin-1 receptors (NK1R) at neural-tumor interfaces[110], to catecholamine-inspired ligands developed to strengthen affinity within adrenergic receptor-dense microenvironments. Another class exploits biomimetic coatings derived from neural cell membranes (for instance, Schwann cells) or from stem cells displaying neural tropism, enabling the carriers to home naturally to tumor niches[111].

Although these neuro-targeted nanocarrier systems hold considerable promise, they face several substantial hurdles in clinical translation. Complex

biological barriers, such as the blood-brain barrier in CNS tumors and the dense stromal matrix surrounding peripheral tumors, frequently restrict the fraction of nanoparticles that successfully reach the intended neural-tumor interface. Off-target binding to healthy nerves remains a safety concern[112,113]. Heterogeneity in receptor expression, including Trk and adrenergic receptors, adds another layer of difficulty because levels differ markedly across patients, tumor types, and disease stages, thereby undermining efforts to devise a universally effective targeting strategy. The reproducible and scalable synthesis of stable ligand-functionalized nanocarriers that maintain consistent pharmacokinetic profiles is technically demanding, and most investigations are still in the proof-of-concept phase, with scant data on long-term safety, immunogenicity, and industrial-scale production. The tumor neural niche undergoes continuous remodeling during disease progression and therapeutic intervention, which can shift the accessibility and performance of these carriers over time.

Therefore, while neuro-targeted nanocarriers represent a rational and actively researched direction, overcoming these biological, engineering, and translational barriers is essential for their successful clinical application. Future efforts should integrate multi-omics profiling to identify robust targeting signatures, develop smart carriers responsive to the local microenvironment, and employ combination strategies to enhance their penetration and efficacy.

Notably, a major bottleneck in advancing neuromodulatory therapies to the clinic is the scarcity of reliable biomarkers for patient stratification. Integrating neuro-specific markers, such as NGF expression or β2-adrenergic receptor density, with immune indicators such as PD-L1 positivity on neural elements, could provide robust predictive power for treatment response. In prostate cancer, for instance, elevated PD-L1-positive neural density has been linked to enhanced immunotherapy outcomes, thereby offering a

practical framework for biomarker development[114].

Although most mechanistic insights into cancer neuroscience continue to be derived from preclinical models, early phase clinical translation has begun to emerge. For example, combinations such as propranolol plus pembrolizumab have entered clinical testing (NCT03384836), and ongoing or subsequent studies (e.g., NCT05741164) further highlight the need for adequately powered Phase II and III trials to define the optimal dosing, timing, and patient selection criteria for routine clinical application[115,116]. Furthermore, elucidating the crosstalk between neural signaling and other oncogenic pathways (e.g., MAPK, PI3K) will provide a foundation for rational combination therapies.

Addressing these technical and methodological obstacles is crucial for generating robust and reproducible data that can bridge the gap between mechanistic discovery and the development of effective neuro-targeted clinical interventions. Despite these challenges, promising perspectives and directions, as detailed below, can guide future research in overcoming these barriers and advancing the field.

11. Future Directions

11.1 Refining Neural-Targeted Intervention Strategies

Future therapeutic development must move beyond broad inhibition and focus on precise interventions. Pharmacologically, the repurposing of drugs such as β-blockers (e.g., propranolol) and the development of specific antagonists for receptors such as AMPAR in gliomas or RAMP1 (for CGRP) in immunosuppressive niches show promise in intercepting oncogenic signals. More direct approaches, such as surgical neurectomy (e.g., celiac ganglionectomy) and percutaneous nerve ablation, offer the potential to physically remove a key tumor-supporting axis, with early clinical trials

exploring these modalities. The greatest potential likely lies in combination therapies, where neural-targeting agents are used to sensitize tumors to immunotherapy or chemotherapy by reversing neural-mediated immunosuppression and resistance[117].

11.2 Integrating the Neuro-Endocrine-Immune Network

To effectively integrate the neuroendocrine-immune axis into cancer therapy, a multidimensional strategy is required. This involves moving beyond isolated interventions and designing treatments that concurrently modulate signals across all three systems to disrupt the pro-tumorigenic network and restore immune competence[118].

11.2.1 Simultaneous Multi-System Targeting

Therapeutic regimens should combine agents that target distinct nodes of this axis. For instance, a regimen might pair a β-blocker (to inhibit sympathetic/adrenergic signaling) with a glucocorticoid receptor modulator (to mitigate stress-induced endocrine effects) and an immune checkpoint inhibitor (to reinvigorate the suppressed T cell response). This approach aims to dismantle the immunosuppressive cascade at multiple levels, preventing compensatory pathways from sustaining a tumor-promoting environment[63].

11.2.2 Exploiting Bidirectional Communication for Amplified Effects

Interventions can be designed to leverage the inherent feedback of the axis. Activating the cholinergic anti-inflammatory pathway (e.g., through vagus nerve stimulation or specific α7nAChR agonists) can systemically reduce inflammatory cytokines, which may dampen sympathetic tone and create a more permissive context for immunotherapy. This represents a "top-down" systems-level intervention to reset the host physiological state[119].

11.2.3 Biomarker-Driven Patient Stratification

Treatment selection should be guided by profiling an individual's axis activity. Patients exhibiting biomarkers of chronic stress (e.g., elevated salivary cortisol and high circulating catecholamines), high intratumoral nerve density, and a myeloid-rich immunosuppressive microenvironment are prime candidates for integrated neuroendocrine-immune therapy. This precision approach ensures that interventions are directed at the dominant mechanisms fueling a patient's specific disease[120].

11.2.4 Temporal and Contextual Considerations

Therefore, therapeutic strategies must be adapted to the dynamic nature of the axis. For example, the perioperative period is a critical window for stress and inflammatory disruption, and the preemptive use of β-blockers and anti-inflammatory agents could potentially prevent metastatic seeding. During immunotherapy, concomitant neuromodulation can be used to precondition the microenvironment and break initial resistance[118]. Furthermore, non-pharmacological interventions, such as stress-reduction therapies (e.g., mindfulness and exercise), could serve as adjuncts to normalize the systemic neuroendocrine milieu and improve therapeutic outcomes.

Overall, integrating the neuroendocrine-immune axis requires a paradigm shift from single-target to system-level therapeutics. By designing combination strategies that concurrently modulate neural output, hormonal influence, and immune function, and tailoring these strategies to individual patient pathophysiology, we can more effectively disrupt the comprehensive biological network that supports cancer progression.

12. Conclusion

In summary, neuron–tumor crosstalk represents a pivotal yet underappreciated axis in cancer biology, profoundly remodeling the local

microenvironment, disrupting immune homeostasis and neuroendocrine regulation, and rewiring systemic metabolic reprogramming—ranging from adipokine-mediated endocrine routes to direct organelle-level mitochondrial transfer. Beyond driving tumor proliferation, invasion, metastasis and therapeutic resistance, tumor neuron hijack acts as a central upstream driver linking neural dysregulation to niche remodeling, host systemic perturbation, and the persistence of cancer-associated pain, which in turn fuels a feed-forward loop that further amplifies neural dysregulation and accelerates tumor progression. We define this pathological rewiring and neural circuit subversion as tumor neuron hijack, a sophisticated malignant strategy analogous to immune escape. By commandeering neural networks, tumors actively reshape the tumor niche and remodel the host macroenvironment, systematically deceiving and co-opting neural circuits to maintain an immune-suppressive, growth-permissive ecosystem. These insights support the clinical translation of neuromodulatory strategies, including repurposed neurotrophic agents, synaptic blockade, and neural signal reprogramming, especially in combination with immunotherapy, offering a promising new direction for precision oncology and palliative pain management.

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Generative AI Use

Certain figures in this manuscript (including Figure 1, Figure 2, Figure 3, Figure 4, and Figure 5) were initially created with the assistance of generative artificial intelligence tools. All AI-generated content was subsequently reviewed, manually redrawn, and finalized by the authors using Adobe Illustrator to ensure scientific accuracy, precision, and compliance with journal standards.

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Authors' contributions

BJ and LZ contributed equally to this work. They were responsible for conceptualization, literature review, drafting the original manuscript, preparation of figures and tables, and integration of the tripartite framework. MT, NX, YH, and XL participated in the systematic literature search, curation of references, and drafting of selected sections (particularly Sections 2 and 4). GY, QW, ZS, HYK, HS, and KX provided critical revisions, intellectual guidance, and supervision throughout the project. All authors read and approved the final version of the manuscript.

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Table, figure legends

Table 1: Core Mechanisms of the Neuro-Immuno-Tumor Tripartite Crosstalk

Table 2: Drug Intervention-Related Information in Neuromodulatory Therapies

Figure 1. Comparison of Neural Recruitment Mechanisms in CNS vs Peripheral Tumors. This schematic contrasts the distinct neural recruitment and interaction strategies employed by central nervous system (CNS) tumors (left panel) and peripheral tumors (right panel). In CNS tumors (e.g., gliomas), tumor cells integrate into pre-existing neural networks through synaptic integration, vessel co-option, and activity-regulated secretion involving molecules such as neuroligin-3 (NLGN3). In peripheral tumors, de novo innervation occurs via nerve fiber recruitment mediated by axon guidance molecules (e.g., netrins and semaphorins), neurotrophin (NT) signaling (including catecholamines and acetylcholine [ACh]), and neuro-immune modulation. Arrows indicate signaling/cellular interactions (solid) and recruitment processes (dashed). This schematic was manually prepared

and refined in Adobe Illustrator. All molecular structures, signaling pathways, and scientific details were verified and corrected by the authors based on the primary literature.

Figure 2. Distinct Neurotransmitter Signaling Pathways in CNS and Peripheral Tumors. These schematic contrasts the distinct neural-tumor interaction strategies in central nervous system (CNS) tumors (left panel) and peripheral tumors (right panel). The left panel illustrates the integration of glioma cells into pre-existing neuronal circuits of the CNS through electrochemical coupling, neurotransmitter-synaptic integration (e.g., glutamate signaling via AMPA receptors [AMPAR]), calcium transients, and P2X receptor-mediated signaling, ultimately leading to CREB/mTOR activation and network synchronization that drives tumor proliferation. In contrast, the right panel depicts de novo innervation in peripheral tumors, mediated by cholinergic nerves releasing acetylcholine (ACh) acting on muscarinic/nicotinic acetylcholine receptors (AChR) and adrenergic nerves releasing norepinephrine (NE) acting on β-adrenergic receptors (β-AR), which converge on downstream pathways such as MAPK/ERK to promote tumor growth, invasion, and survival. This schematic was manually prepared and refined in Adobe Illustrator. All molecular structures, signaling pathways, and scientific details were verified and corrected by the authors based on the primary literature.

Figure 3. Interactions within the tumor microenvironment. Neuronal activity orchestrates tumor progression through bidirectional crosstalk with immune cells, particularly $CD8^+$ T cells. In the sympathetic nervous system, norepinephrine (NE) released from local nerve fibers activates β2-adrenergic receptors (β2-AR) on tumor cells and immune cells (including $CD8^+$ T cells, tumor-associated macrophages [TAMs], and myeloid-derived suppressor cells [MDSCs]), triggering the cyclic adenosine monophosphate/protein kinase A/signal transducer and activator of transcription 3 (cAMP/PKA/STAT3)

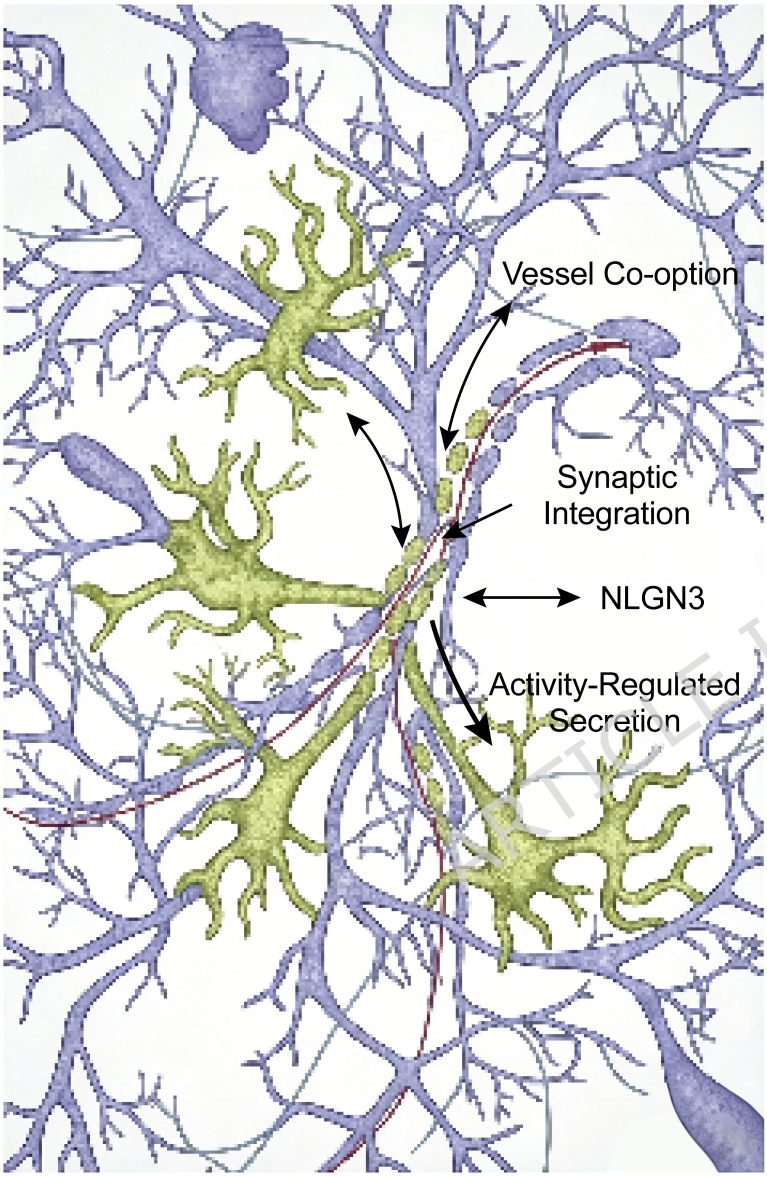
signaling pathway. This leads to MDSC recruitment (via CCL2/CXCL chemokines), M2-like TAM polarization, and $CD8^+$ T-cell exhaustion, establishing the “neural–MDSC–T cell” immunosuppressive axis described in this section. This mechanism is further exemplified in gliomas, where additional neurotransmitter receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], N-methyl-D-aspartate [NMDA], cholinergic, and gamma-aminobutyric acid [GABA]) and gap junction networks amplify the neuron–glioma–immune feedback loop, promoting both immune evasion and tumor-intrinsic excitability. Druggable targets (e.g., neurokinin 1 receptor [NK1R], nerve growth factor receptor [NGFR], vasoactive intestinal peptide receptor [VIPR], and receptor activity-modifying protein 1 [RAMP1]) and repurposed drugs (e.g., β-blockers, atropine, memantine, and rimegepant) highlight the therapeutic potential of disrupting the neuro-immune synapse. This schematic was manually prepared and refined in Adobe Illustrator. All molecular structures, signaling pathways, and scientific details were verified and corrected by the authors based on the primary literature.

Figure 4. Comprehensive map of neurotransmitter signaling in cancer. Structural neuro-immune synapses (e.g., sensory nerve–$CD8^+$ T cell contacts enabling polarized calcitonin gene-related peptide–receptor activity-modifying protein 1 [CGRP-RAMP1] signaling) and spatial interactions converge on intracellular signaling networks within tumor and immune cells. Key neurotransmitter receptors, including muscarinic/nicotinic cholinergic, gamma-aminobutyric acid A/B (GABA_A/B), dopamine receptors (DRD1/2/5), 5-hydroxytryptamine receptors (5-HTRs), metabotropic glutamate receptor 1 (mGluR1), and CGRP-RAMP1, along with other neural-derived signals, activate downstream cascades such as Wnt/β-catenin, Notch, epidermal growth factor receptor (EGFR)/phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), extracellular signal-regulated kinase 1/2 (ERK1/2), and cAMP response element-binding protein (CREB). These pathways collectively drive regulatory T cell (Treg) expansion,

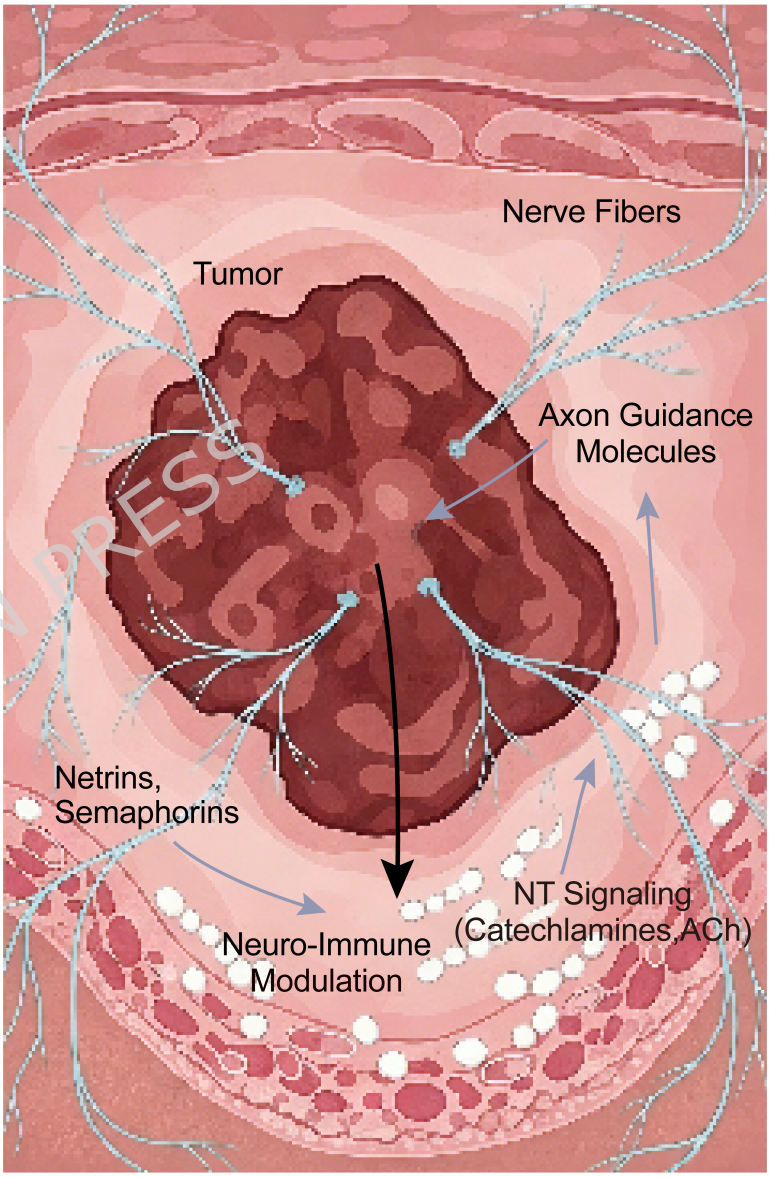
CD8$^+$ T-cell exhaustion, M2-like tumor-associated macrophage (TAM) polarization, secretion of immunosuppressive cytokines (e.g., interleukin-10 [IL-10], transforming growth factor-β [TGF-β], IL-6, and vascular endothelial growth factor [VEGF]), metabolic reprogramming, invasion, and therapeutic resistance. Pharmacological modulators (e.g., baclofen for GABA_B receptor and ifenprodil for mGluR1) highlight therapeutic opportunities. Tumor-derived exosomes (as described in the text) can feed into these networks via nerve growth factor (NGF) and other mediators. This schematic was manually prepared and refined in Adobe Illustrator. All molecular structures, signaling pathways, and scientific details were verified and corrected by the authors based on the primary literature.

Figure 5. Tumor-targeted nanocarrier platforms for analgesic delivery in the neuro-oncology axis. Tumor-targeted nanocarriers functionalized with specific ligands enable selective intratumoral accumulation of therapeutics while minimizing systemic exposure. The left panel depicts the tumor microenvironment with perineural invasion, showing cancer cells interacting with infiltrating sympathetic and sensory nerves. Key pathways include NGF/TrkA signaling that drives nociceptor sensitization and perineural invasion, as well as CGRP release that promotes tumor progression and CD8$^+$ T-cell exhaustion. The right panel illustrates a ligand-functionalized nanoparticle nanocarrier equipped with an anti-NGF/TrkA antibody, a substance P (Substance-P) analog, and a TRPV1 antagonist, achieving high intratumoral accumulation with minimal systemic toxicity. This schematic was manually prepared and refined in Adobe Illustrator. All molecular structures, signaling pathways, and scientific details were verified and corrected by the authors based on the primary literature.

CNS Tumors



Peripheral Tumors



Arrows:

- ● Signaling/Cellular
- ⟶ Interactions
- - - ➤ Recruitment Process

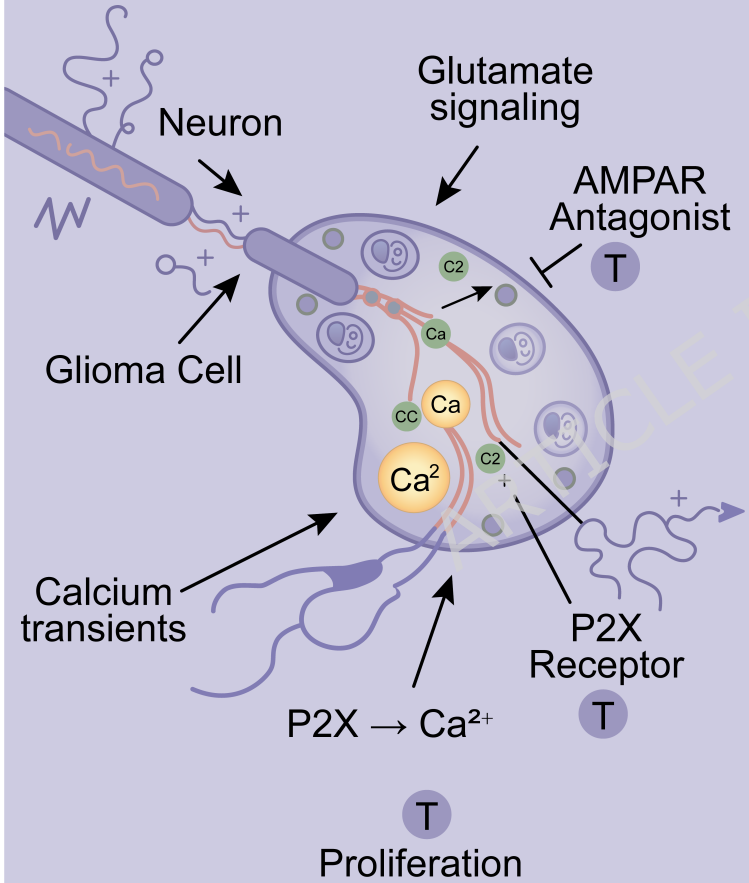
Specific Molecules:

-NLGN3
-Netrins
Semaphorins
Catecholamines
ACh

Neuro-Tumor Interactions: Signaling Mechanisms

Central Nervous System (CNS)
Electrochemical coupling

Neurotransmitter-Synaptic integration



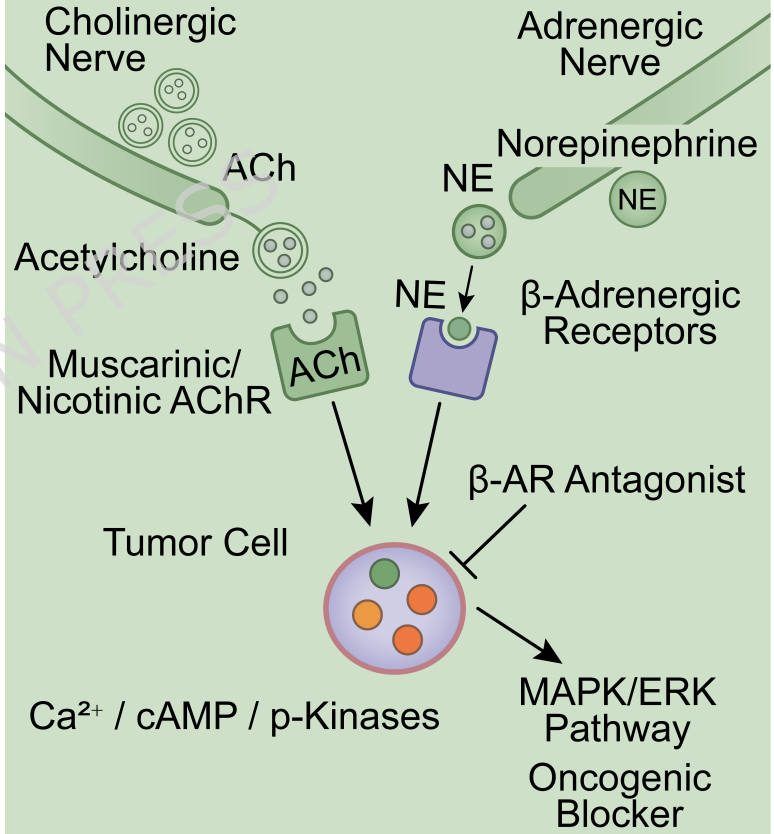
CREB/mTOR → Proliferation

Network synchronization

Neuro-Tumor Interactions & Therapeutic Targets

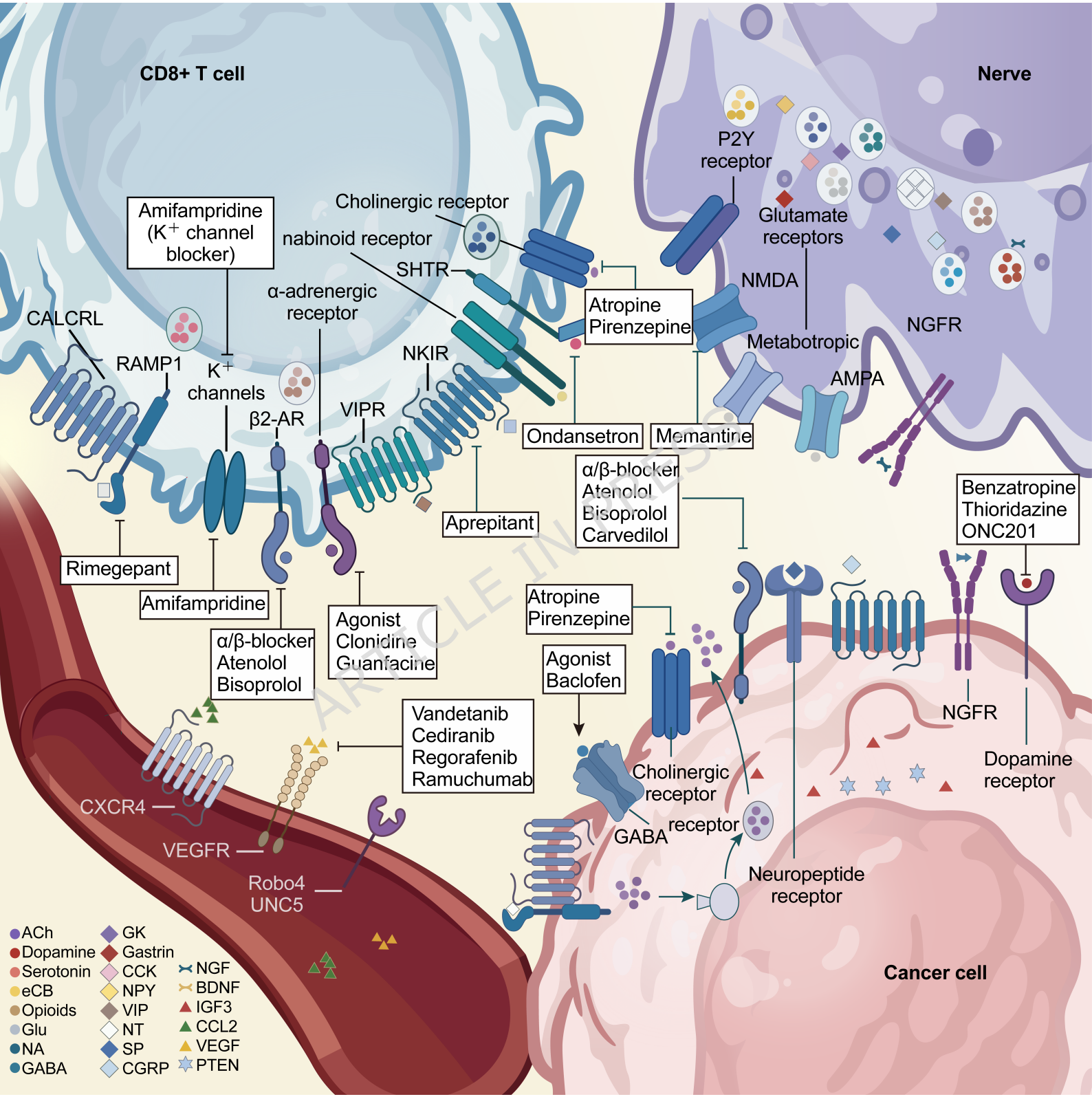
Neurotransmitter-receptor mediated signaling

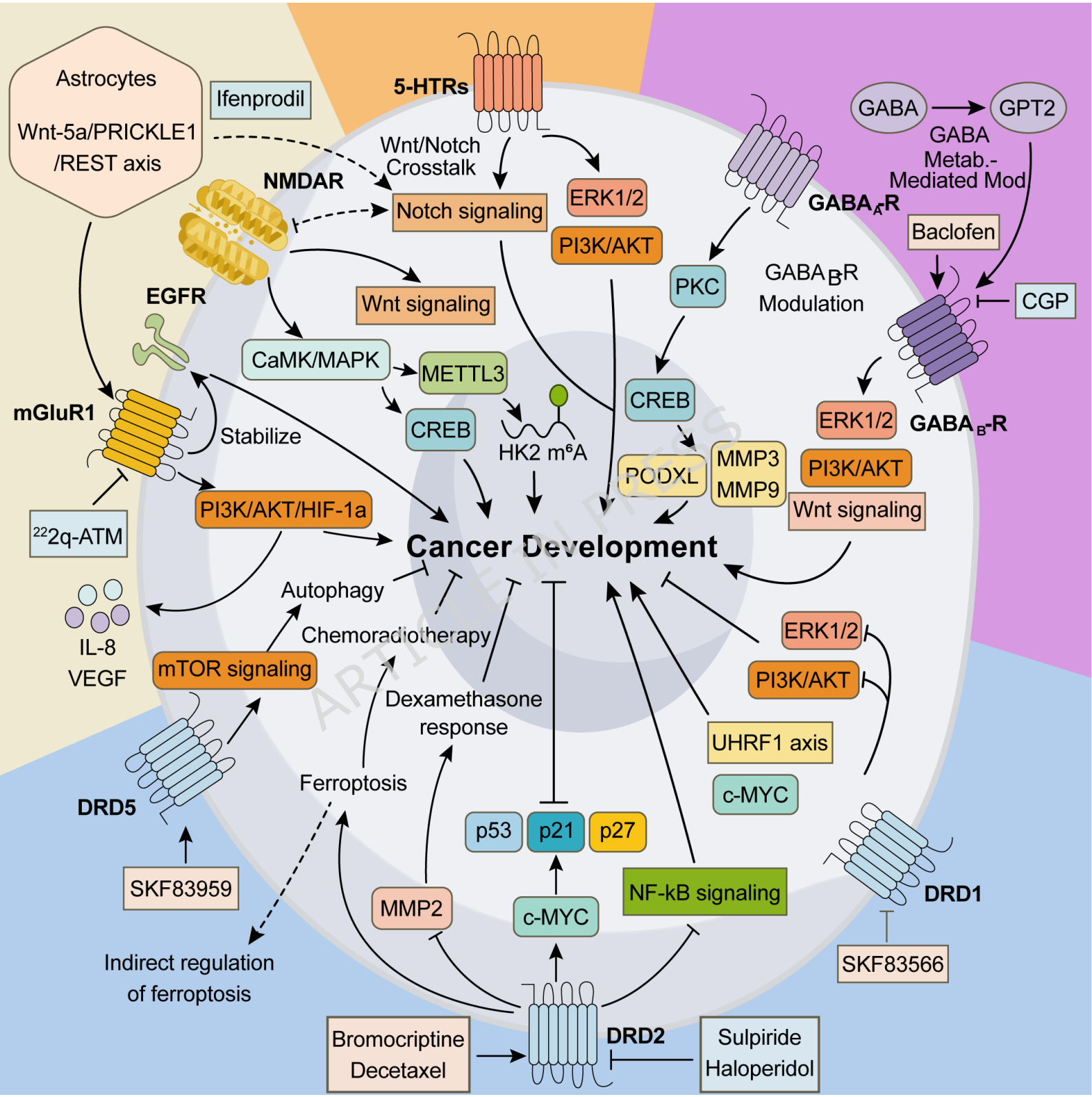
Peripheral Tumors



MAPK → Invasion / Survival / Proliferation

Tumor Growth




Astrocytes
Wnt-5a/PRICKLE1
/REST axis
Ifenprodil
5-HTRs
Wnt/Notch
Crosstalk
NMDAR
Notch signaling
ERK1/2
PI3K/AKT
GABA
GPT2
GABA
Metab.-
Mediated Mod
GABA$_A$R
Baclofen
PKC
GABA$_B$R
Modulation
CGP
EGFR
Wnt signaling
CaMK/MAPK
METTL3
CREB
HK2 m^{6}A
CREB
ERK1/2
GABA$_B$-R
mGluR1
Stabilize
PODXL
MMP3
MMP9
PI3K/AKT
Wnt signaling
PI3K/AKT/HIF-1a
^{22}2q-ATM
Cancer Development
Autophagy
IL-8
VEGF
Chemoradiotherapy
ERK1/2
PI3K/AKT
mTOR signaling
Dexamethasone
response
UHRF1 axis
c-MYC
DRD5
Ferroptosis
p53
p21
p27
SKF83959
NF-kB signaling
DRD1
MMP2
c-MYC
SKF83566
Indirect regulation
of ferroptosis
Bromocriptine
Decetaxel
DRD2
Sulpiride
Haloperidol

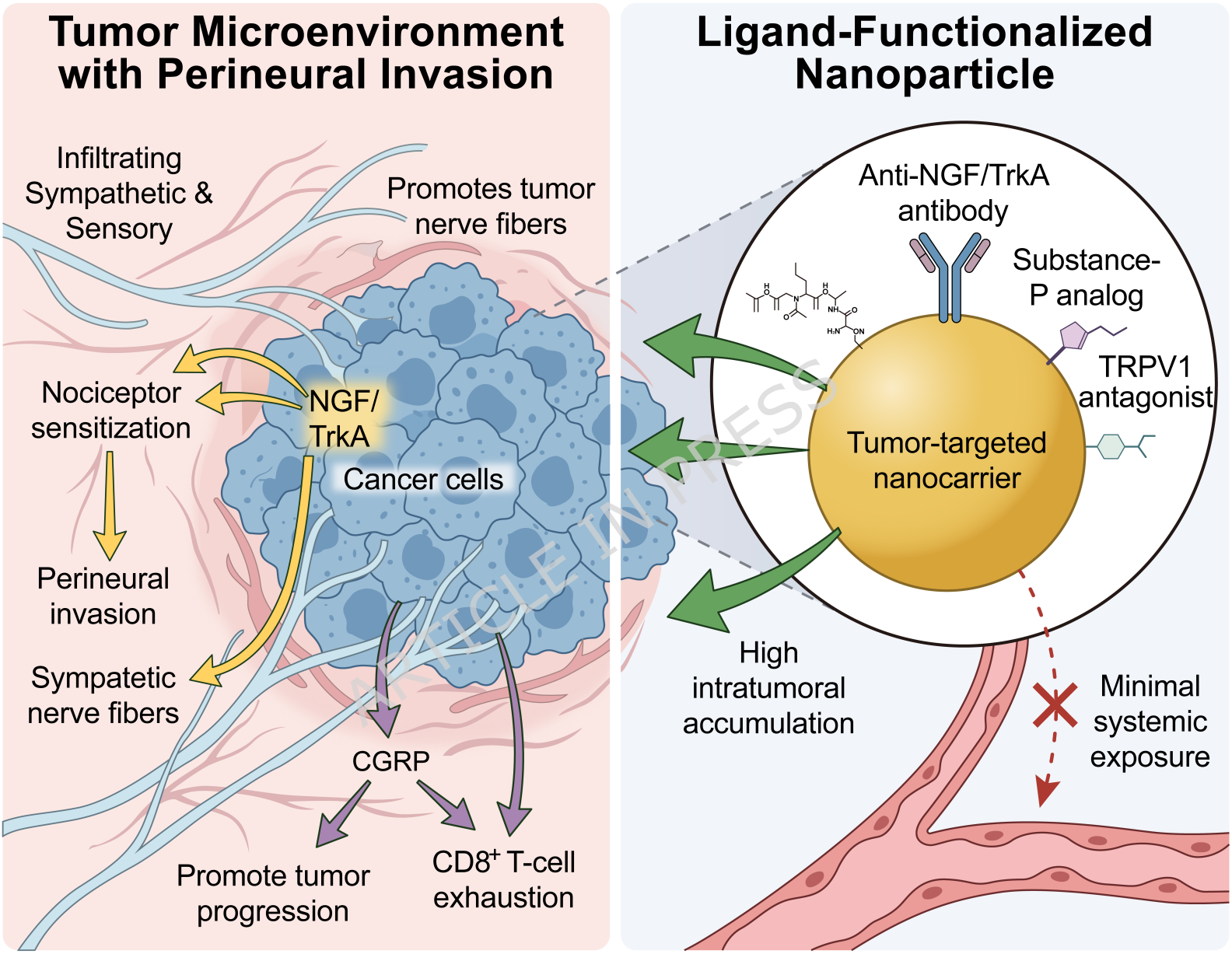


Table 1: Core Mechanisms of the Neuro-Immuno-Tumor Tripartite Crosstalk

anism Category	Key Mediators & Pathways	Biological & Clinical Implications
ral Recruitment Architecture	Neurotrophic Factors: *NGF, BDNF, GDNF;* Axon Guidance: *Netrin-1, SLIT2,* Semaphorins; Receptors: *TrkA/B/C, p75NTR,* Neuropilin.	Neoneurogenesis: Tumor-induced nerve sprou ting; Perineural Invasion (PNI): Migration along ne ural highways; Synaptic Integration: Formation of neo-synapses (in CNS tumors).
Tumor Modulation	Neurotransmitters: Glutamate, Norepinephrine (NE), Acetylcholine (ACh); Receptors: AMPAR, *ADRB2 , CHRM ;* Pathways: Ca^{2+} influx, cAMP/PKA, PI3K/AKT, MAPK.	Oncogenic Signaling: Activation of *CREB/mTO R* driving proliferation; Therapy Resistance: Enhanced survival and c hemoresistance; Metabolic Symbiosis: Lactate shuttle between neurons and tumor cells.
e Microenvironme nt Remodeling	Sympathetic Axis: NE → ADRB2→ PKA/STAT3 → *CCL2/CXCL;* Sensory Axis: CGRP → *RAMP1*, Substance P; Immune Cells: MDSCs, M2-like TAMs, Tregs, Exhausted $CD8^+$ T cells.	Immunosuppression: Inhibition of $CD8^+$ T cell cytotoxicity; Immune Evasion: Polarization of M2-like TAMs and Treg expansion; "Cold Tumor" Phenotype: Exclusion of cytotox ic lymphocytes.
l & Vascular Remo deling	Angiogenic Factors: *VEGF*, Angiopoietin; Neuro-Vascular Mimicry: Co-option of vascular networks; Stromal Cells: CAFs, Endothelial cells.	Angiogenesis: Neuro-vascular coupling providing nutrient supply; Matrix Stiffness: CAF activation and ECM remodeling; Metastatic Niche: Preparation of pre-metastat ic sites via neural signals.
emic Regulation	HPA Axis: Cortisol/Corticosterone; SNS Output: Circulating Catecholamines; Host Metabolism: Lipolysis, Glycolysis.	Systemic Immunosuppression: Impaired NK cell and dendritic cell function; Tumor Promotion: Stress-induced mobilization of ene rgy substrates (glucose/FFAs); Therapeutic Barrier: Induction of a systemic pro-tumorigenic state.

Table 2: Drug Intervention-Related Information in Neuromodulatory Therapies

Drug/Intervention	Targeted Neural Signal Type	Primary Oncology Indications	Clinical Trial Status/Key Findings	Main Reference
Propranolol(non-selective β-blocker)	β2-adrenergic receptor(ADRB2)	Breast cancer	Reduces lymph node metastasis by 47%in breast cancer patients;enhances efficacy of immune checkpoint inhibitors with immunomodulatory effects	*91*
Darifenacin/Solifenacin(M3R antagonists)	Muscarinic acetylcholine receptor(CHRM3/M3R)	Gastric cancer	Effectively inhibits tumor growth in gastric cancer	*28*
Bethanechol(cholinergic agonist)	Muscarinic acetylcholine receptor(CHRM1)	Pancreatic cancer	Delays progression of PanIN to invasive cancer in preclinical models	*95*
Tanezumab(anti-NGF monoclonal antibody)	NGF/TrkA pathway	Bone metastasis-associated cancer pain	Phase III trial:clinically meaningful pain reduction;attenuates nerve sprouting and neuroma formation(development discontinued)	*97*
CGRP receptor antagonists(e.g.,rimegepant or olcegepant analogs)	Sensory nerve CGRP pathway	Melanoma,osteosarcoma	Preclinical:reverses $CD8^+$T-cell exhaustion,reduces pain scores,and attenuates tumor progression and angiogenesis	*98*