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Review

Cancer Neuroscience: From Innervation-Specialized Microenvironments to Ecological Therapy and Brain–Body Crosstalk

Hao-Ran Dang[1], Ming-Zhu Jin[2,3,*], Wei-Lin Jin[1,*]

[1]Institute of Cancer Neuroscience, Medical Frontier Innovation Research Center, The First Hospital of Lanzhou University, The First Clinical Medical College of Lanzhou University, 730000 Lanzhou, Gansu, China
[2]Department of Obstetrics and Gynecology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, 200017 Shanghai, China
[3]Shanghai Key Laboratory of Gynecologic Oncology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, 200017 Shanghai, China
*Correspondence: mingzhujin@sjtu.edu.cn (Ming-Zhu Jin); ldyy_jinwl@lzu.edu.cn; weilinjin2026@163.com (Wei-Lin Jin)
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Abstract

Cancer neuroscience has revealed that neural activity can actively influence tumor progression. This review synthesizes advances from 2024–2026 within a three-pillar framework: the innervation-specialized microenvironment (iSME), ecological therapy, and brain–body crosstalk. Locally, tumors recruit neural inputs. In certain tumor contexts, neurons form glutamatergic synapse-like contacts with cancer cells or transfer mitochondria to them, contributing to a metabolically active iSME. At the systemic level, experimental studies implicate circuits such as a vagal sensory–sympathetic axis, a corticoamygdala pathway associated with social interaction, and a lateral septum–enteric circuit in tumor progression and immune regulation. These findings provide a rationale for investigating circuit-specific interventions. The three highlight emphasize systemic neural influences on cancer and support further investigation of neural-targeting agents (β-blockers, gepants, and aprepitant) in combination with immunotherapy and chemotherapy.

Keywords: tumor microenvironment; neuroimmunomodulation; autonomic nervous system; brain-gut axis; precision medicine

1. Introduction

The relationship between the nervous system and cancer has long been observed in medicine, but its role in tumor biology has only recently come into focus. Nearly two centuries ago, the French anatomist Jean Cruveilhier documented a mammary tumor extending along the facial nerve—an observation that would remain mechanistically unexplained for generations [1]. Today, that clinical vignette stands as a historical anchor for cancer neuroscience, which interrogates how neurons, glia, neurotransmitters, and neural circuits interact with cancer cells and influence malignant behavior [2,3]. The field has matured rapidly, evolving from isolated clinical observations into a mechanistically rigorous discipline within a single decade [4,5,6].

For much of the twentieth century, oncology conceived of the tumor as a largely autonomous cellular mass shaped by somatic mutations and clonal selection. The tumor microenvironment (TME) was subsequently recognized as an active contributor, encompassing immune cells, fibroblasts, and endothelial cells. Yet most conceptual frameworks still omitted the nervous system. This omission reflected a historical assumption that neural tissue was a passive bystander, present by anatomical coincidence rather than functional necessity. However, a series of seminal studies over the past decade has decisively overturned this assumption. Autonomic nerve density predicts prostate cancer progression [7], neural progenitors are recruited from the central nervous system to fuel tumor-associated neurogenesis [8], and cancer cells actively reprogram peripheral neurons to promote invasion [9,10]. The publication of a formal roadmap for cancer neuroscience in Cell in 2020 consolidated this direction by cataloguing the spectrum of mechanisms by which tumors "hijack" the nervous system—from commandeering metabolic resources to reprogramming neuronal identity [2,4,5].

The demonstration that autonomic nerves actively drive prostate cancer progression marked a pivotal shift from viewing nerves as passive bystanders to active participants in tumorigenesis [7]. Further causal evidence came from studies showing that vagal denervation suppresses gastric tumor growth [11], and by the discovery that glioma cells functionally integrate into neural circuits through bona fide glutamatergic synapses [12,13]. These studies helped establish the nervous system as a functional constituent of the tumor microenvironment—a concept now formally recognized as an emerging hallmark of cancer [14,15].

Three related lines of research organize this review. The first pillar concerns tumor innervation and the innervation-specialized microenvironment (iSME): a local niche in which tumors recruit and remodel peripheral nerve fibers and interact with them. Unlike the passive co-option of pre-existing nerves, tumor-driven neo-innervation involves secretion of axon-guidance molecules, neurotrophic factors, and extracellular vesicles that promote axonal sprouting into the tumor. Tumor-associated neurogenesis can also involve the recruitment of neuronal progenitors

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[16,17]. Recent discoveries have profoundly expanded this pillar, revealing that neurons can form functional glutamatergic synapse-like contacts with cancer cells or transfer mitochondria through tunneling nanotubes, while Schwann cells can provide metabolic support [18,19,20,21].

The second pillar encompasses the ecological therapy of cancer. This framework treats the tumor as a dynamic ecosystem embedded in the body's physiological environment. Tumors function as "signal hijackers" that exploit chemical, electrical, and mechanical communication systems to construct a self-serving ecosystem [22]. This perspective suggests that therapeutic strategies could address systemic neural and neuroendocrine influences alongside tumor cells. Recent circuit-specific studies support this view: for example, social interaction reduced breast tumor growth through a defined corticoamygdala circuit in experimental models [23], whereas colorectal cancer co-opts a lateral septum–enteric circuit [24]. These findings provide a rationale for testing interventions directed at defined neural circuits.

The third, and perhaps most expansive, pillar concerns brain–body crosstalk. This pillar examines how the brain, autonomic nervous system, and psychosocial states influence peripheral tumors and how tumors, in turn, alter central physiology [25,26]. This systemic axis has gained unprecedented mechanistic clarity from two recent studies. One demonstrated that tumors communicate with the brain via ascending sensory afferents, which in turn activate sympathetic outflow to systemically suppress anti-tumor immunity through a defined vagal sensory–sympathetic pathway [27]. Another study revealed that sensory neurons within the breast cancer TME actively promote immune exclusion by inducing a dense, immunosuppressive extracellular matrix [28]. These studies show that anatomically defined pathways can influence immune evasion, although their contribution varies with tumor context.

Cancer neuroscience has grown rapidly. The concept of the iSME, first articulated in 2020, provided a spatial and mechanistic scaffold for understanding how neural inputs are transduced into oncogenic outputs [29]. Subsequent reviews—from the "war of nerves" perspective [4], to the translational roadmap [5], to the state-of-the-field assessment by Winkler and colleagues [6], and the most recent horizon-scanning by Monje and Winkler [30]—collectively document a field in rapid maturation. Hanahan and Monje have further proposed that neuronal and glial interactions constitute an emerging hallmark of cancer, placing the nervous system alongside immune evasion and metabolic reprogramming as a fundamental dimension of malignancy [14,31]. Subsequent studies have reported functionally important neural interactions in several tissue contexts, from pancreatic ductal adenocarcinoma (PDAC) and prostate cancer to triple-negative breast cancer and cholangiocarcinoma [5,6].

The three-pillar framework is an organizing principle whose application depends on tumor context [6,32]. In primary central nervous system (CNS) tumors such as glioma, Pillar I principally concerns integration into pre-existing neural circuits (e.g., glutamatergic synapses and NLGN3 signaling) [12,18]. In peripheral cancers such as PDAC, prostate cancer, and head and neck squamous cell carcinoma (HNSCC), it involves tumor-driven neo-innervation, axon guidance, perineural invasion, and metabolic coupling [7,16,33,34]. Pillars II and III apply to both, but the dominant mechanisms and therapeutic nodes differ. Thus, the relative weight of the three pillars varies by tumor context rather than being identical across cancers [14].

Within this three-pillar framework, Pillar II (ecological therapy) conceptualizes the tumor as an ecosystem embedded within systemic neural, endocrine, and immune networks, emphasizing the dynamic and multifactorial nature of tumor–host interactions. Pillar III (brain–body crosstalk) examines the neural circuits that contribute to these interactions. Accordingly, Pillar II emphasizes therapeutic strategies, while Pillar III examines circuit-level mechanisms in greater detail.

The field's rapid maturation is reflected in a series of authoritative syntheses published in the past two years. Comprehensive overviews have traced the arc from historical roots to current frontiers and catalogued progress across cancer types [6,35], while the core principles have been distilled into the essential neuroscience of cancer [3]. The neuro-immune axis has been systematically reviewed [36], and the therapeutic landscape has been mapped to catalogue a growing arsenal of neural-targeted interventions [37]. A recent conceptual account also considers cancer a systemic disease involving neural interactions, circadian disruption, and microbiome-mediated ecology [38].

The translational implications of this enterprise are substantial. Perineural invasion, the spread of cancer cells along nerve sheaths, is an independent predictor of poor prognosis in pancreatic, head and neck, and colorectal cancers [39]. Neural density within tumors correlates with metastatic potential and patient survival [7,40]. Stress-induced adrenergic signaling accelerates tumor progression and blunts immunotherapy responses [41]. Furthermore, the discovery that neurons physically transfer mitochondria to cancer cells via tunneling nanotubes endows metastatic cells with enhanced oxidative metabolic capacity [19]. These observations motivate investigation of neural-targeted interventions, including beta-adrenergic blockade, neuropeptide receptor antagonism, and vagus nerve stimulation, as possible complements to established oncological treatments [41,42].

Experimental studies implicate chronic stress-induced adrenergic signaling, immune suppression, and angiogenesis in the stress–cancer connection [43]. Concurrently, glucocorticoids have been shown to promote breast cancer metastasis through receptor-mediated mechanisms, war-

ranting context-specific investigation of corticosteroid exposure in oncology [44]. Complementing this, the sympathetic nervous system induces a metastatic switch in primary breast cancer, establishing a causal link between adrenergic signaling and metastatic dissemination [26]. More broadly, the diverse mechanisms of neural signaling in cancer, ranging from synaptic communication to paracrine neurotransmitter release, have been comprehensively synthesized [45].

Given the breadth of the literature, this review is selective rather than exhaustive. Instead, it seeks to conceptually integrate the field through the three interconnected pillars described above (see Graphical Abstract). First, we examine how tumors acquire neural inputs and how the neural TME is organized (Pillar I). We then consider ecological approaches targeting systemic neural and neuroendocrine influences (Pillar II). Finally, we address communication between the central nervous system and peripheral tumors, including neural regulation of immunity and psychoneuroimmunological pathways (Pillar III) (Fig. 1). This synthesis identifies mechanistic advances, translational opportunities, and questions for future cancer neuroscience research.

2. Tumor Innervation and the Innervation-Specialized Microenvironment (iSME)

Tumor-associated nerves can actively reshape the TME. This first pillar of cancer neuroscience addresses the local interface where nerve fibers, cancer cells, stromal elements, and immune cells interact. Understanding how tumors acquire neural inputs, which nerve types are involved, and how the resulting niche is organized may guide the development of targeted therapies.

2.1 Mechanisms of Tumor Neo-Innervation

Tumors can acquire neural inputs through coordinated signaling between cancer cells, stromal cells, and the peripheral nervous system. The classical framework identified three principal mechanisms: axonal sprouting driven by tumor-secreted neurotrophic factors, neurogenesis from recruited progenitor cells, and neuron reprogramming mediated by cancer-derived extracellular vesicles. Recent work has substantially expanded this framework, revealing new molecular mediators and cellular participants.

Several triggers of tumor neo-innervation have been identified. Endoplasmic reticulum (ER) stress in cancer cells has been identified as a key initiator: ER stress upregulates neurotrophic factor secretion, promoting axonal sprouting toward the tumor. Nutritional deprivation represents a second trigger—pancreatic cancer cells under serine starvation selectively produce nerve growth factor to attract innervation, thereby securing an exogenous supply of serine from neurons [21]. Cancer-derived exosomes constitute a third mechanism: exosomes from head and neck cancer cells carry neurotrophic cargo that induces axonogenesis in distant nerve ganglia [16]. Finally, loss of p53 function in head and neck cancer can alter the extracellular vesicles released by cancer cells. These vesicles reprogram nearby sensory neurons toward an adrenergic phenotype that supports tumor progression [46]. These findings suggest that some tumors actively recruit or reprogram neural inputs in response to environmental stress.

Neurotrophic factor-driven axonogenesis was among the first mechanisms to be characterized. Tumors of several types can express elevated levels of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF), which act on cognate receptors on peripheral nerve terminals to promote axonal elongation and directional growth. Emerging evidence highlights the role of exosomal delivery in this process: pancreatic cancer cells package the long noncoding RNA XIST into exosomes, which are transferred to neurons to promote perineural invasion by sponging miR-211-5p and upregulating GDNF [47]. Additionally, the RAB5B-CD109 interplay in KRAS-mutant pancreatic cancer promotes the surface presentation of pro-axonogenic ligands, driving nerve fiber ingrowth specifically in mutant contexts [48]. Complementing this, the PDGF-D/PDGFRβ axis functions as a bidirectional mediator of tumor-nerve crosstalk [49].

Axon-guidance molecules have also emerged as critical regulators. Netrin-1, a bifunctional guidance cue, promotes both pancreatic tumorigenesis and innervation through its receptor neogenin 1 (NEO1) [50]. Netrin-1 expression correlates with intratumoral nerve density and adverse clinical outcomes in pancreatic ductal adenocarcinoma (PDAC), and its genetic or pharmacological disruption reduces innervation and tumor growth. Notably, Netrin-1 exerts pro-neural functions even in precancerous pancreatic intraepithelial neoplasia lesions, indicating that the innervation program is initiated early in the oncogenic sequence [50].

The second mechanism involves the recruitment of neural progenitor cells from the central nervous system. In the tumor models studied, doublecortin-positive progenitors can migrate from the subventricular zone and contribute to intratumoral neurons [8]. The third mechanism—cancer-induced neuronal reprogramming—has become an active area of investigation. For instance, head and neck squamous cell carcinoma cells, through the loss of p53 function, reprogram mature peripheral neurons to adopt an adrenergic phenotype [46].

The recruitment of neural progenitors from the central nervous system has been implicated in cancer-associated neurogenesis through a defined migratory program [8]. Single-neuron profiling has further revealed that pancreatic cancer reprograms the transcriptomic identity of innervating neurons: the Trace-n-seq method, which combines retrograde axonal tracing with single-cell RNA sequenc-

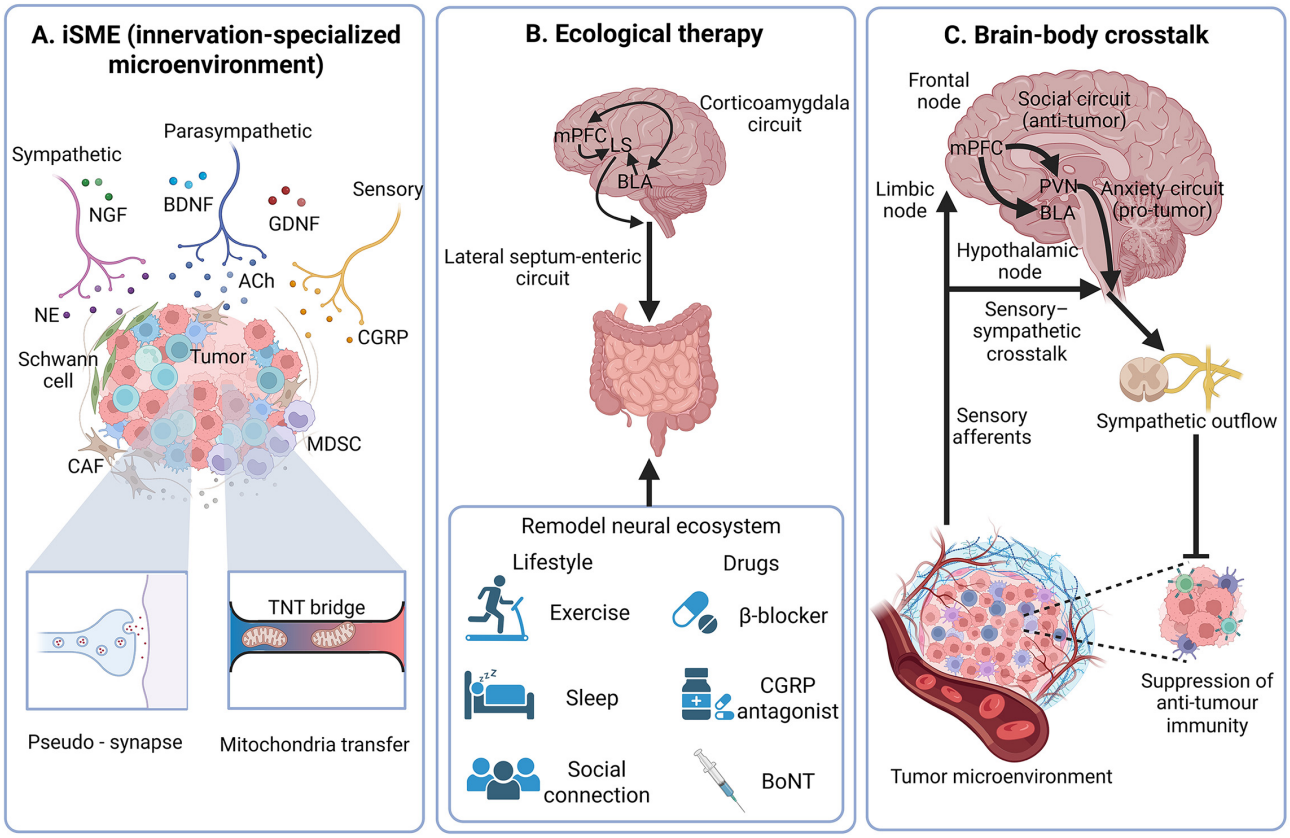

Fig. 1. Conceptual framework of cancer neuroscience: three pillars. Schematic representation of the three integrated pillars defining the field. (A) Pillar I: Tumor innervation and the innervation-specialized microenvironment (iSME). Tumors actively recruit sympathetic, parasympathetic, and sensory nerve fibers through neurotrophic factors, axon-guidance molecules, and extracellular vesicles, establishing a specialized niche comprising Schwann cells, CAFs, and immune cells. (B) Pillar II: Ecological therapy. The tumor is conceptualized as a neural ecosystem susceptible to remodeling by circuit-specific interventions, bodywide physiological modulation, and pharmacological denervation strategies. (C) Pillar III: Brain-body crosstalk. Peripheral tumors communicate with the central nervous system via vagal sensory afferents, activating a vagal sensory–sympathetic pathway that drives sympathetic efferent activity to the lung tumor microenvironment, where β2-adrenergic signaling in alveolar macrophages suppresses antitumor T-cell responses. Neuroendocrine axes (HPA axis) also modulate systemic immunity and metabolism. Bidirectional arrows denote reciprocal regulation, positioning cancer as a systemic neuro-oncological disease. Abbreviations: ACh, acetylcholine; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; BoNT, botulinum toxin; CAF, cancer-associated fibroblast; CGRP, calcitonin gene-related peptide; GDNF, glial cell line-derived neurotrophic factor; HPA, hypothalamic-pituitary-adrenal; iSME, innervation-specialized microenvironment; LS, lateral septum; MDSC, myeloid-derived suppressor cell; mPFC, medial prefrontal cortex; NE, norepinephrine; NGF, nerve growth factor; PVN, paraventricular nucleus; TNT, tunneling nanotube. This figure was created using BioRender (Jin, M. (2026) https://BioRender.com/fgob09r).

ing, has identified distinct neuronal subtypes that are reprogrammed by PDAC and functionally dependent on the tumor microenvironment [10]. Notably, even after surgical tumor resection, the reprogrammed neuronal system retains its pro-tumor phenotype, accelerating the growth of recurrent tumors [10].

2.2 Types and Cancer-Specific Roles of Innervating Nerves

The functional consequences of tumor innervation depend critically on the identity of the nerve fibers. Sympathetic adrenergic, parasympathetic cholinergic, and sensory peptidergic fibers each establish distinct signaling relationships with cancer cells and the TME.

Sympathetic adrenergic innervation has been most extensively studied. In prostate cancer, sympathetic activity promotes tumor growth and metastasis, while parasympathetic activity modulates invasion [7]. Beta-adrenergic signaling activates cAMP, PKA, and extracellular signal-regulated kinase (ERK) pathways that promote cancer cell proliferation, survival, and epithelial-to-mesenchymal transition (EMT), while simultaneously suppressing immune function [41]. Bidirectional crosstalk between sympathetic nerves and cancer-associated fibroblasts (CAFs) further amplifies this dependency by remodeling the extracellular matrix (ECM) [51].

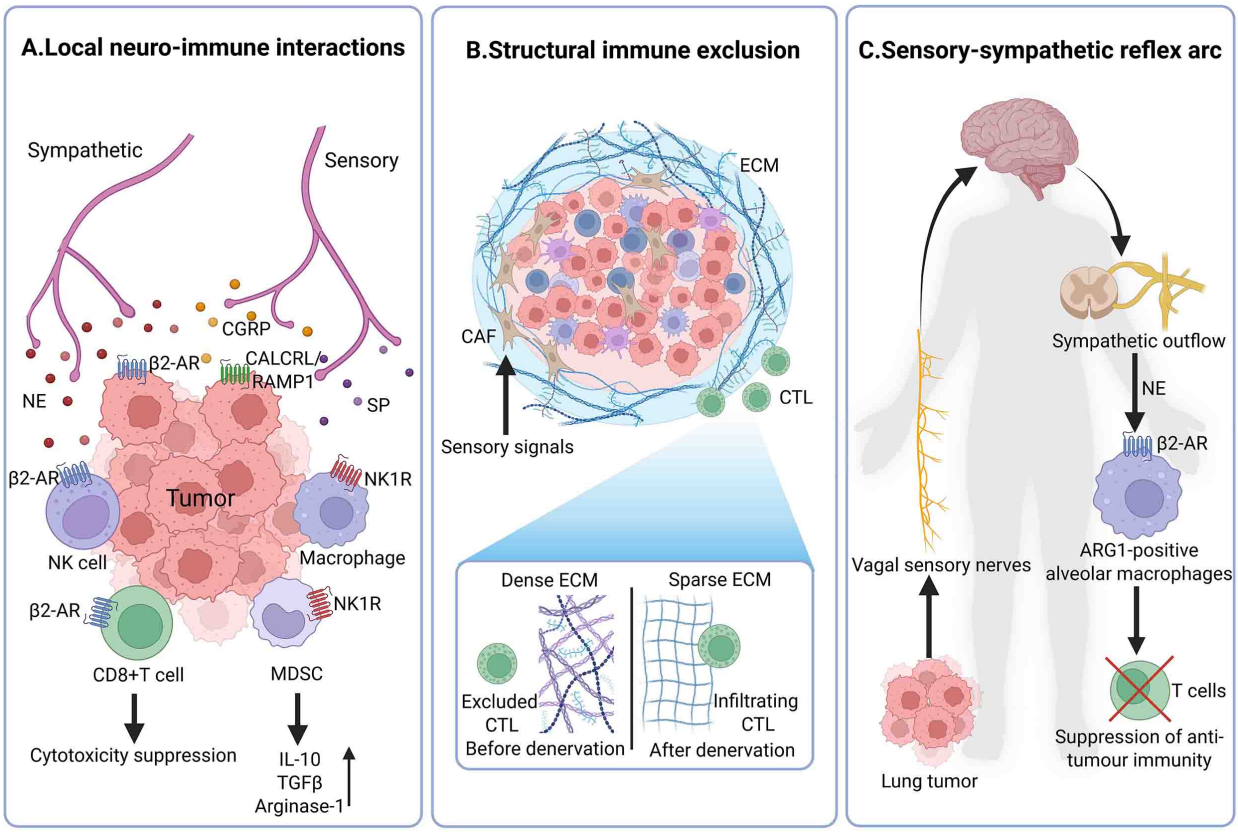

Fig. 2. Neural regulation of the tumor immune microenvironment. Multi-layered mechanisms by which nerve fibers suppress anti-tumor immunity. (A) Local neuro-immune interactions. Sympathetic nerve-derived norepinephrine (NE) activates β2-adrenergic receptors (β2-AR) on NK cells and $CD8^+$ T cells, suppressing cytolytic activity. Sensory nerve-derived CGRP and substance P (SP) suppress cytotoxicity via CALCRL/RAMP1 and NK1R, respectively, while promoting an immunosuppressive macrophage/MDSC phenotype. (B) Structural immune exclusion. Sensory neuron-derived signals stimulate CAFs to deposit a dense, crosslinked ECM that physically obstructs cytotoxic T lymphocyte (CTL) infiltration. (C) Vagal sensory–sympathetic pathway. Tumor-derived signals activate vagal sensory neurons in the nodose ganglia, which project to the nucleus tractus solitarius and rostral ventrolateral medulla in the brainstem; downstream sympathetic efferent activity in the lung tumor microenvironment activates β2-adrenergic signaling in alveolar macrophages, suppressing antitumor T-cell responses. Interruption of this pathway restores anti-tumor immunity. Abbreviations: ARG1, arginase 1; β2-AR, beta-2 adrenergic receptor; CAF, cancer-associated fibroblast; CALCRL/RAMP1, calcitonin receptor-like receptor/receptor activity-modifying protein 1; CGRP, calcitonin gene-related peptide; CTL, cytotoxic T lymphocyte; ECM, extracellular matrix; IL-10, interleukin-10; MDSC, myeloid-derived suppressor cell; NE, norepinephrine; NK1R, neurokinin 1 receptor; SP, substance P; TGFβ, transforming growth factor beta. This figure was created using BioRender (Jin, M. (2026) https://BioRender.com/9zk4zum).

Parasympathetic cholinergic innervation exerts context-dependent effects. In pancreatic cancer, indirect activation of muscarinic receptors can inhibit tumor growth and tumor-associated inflammation, in contrast, vagotomy enhances tumor-associated inflammation and exerts a tumor-promoting effect [52,53]. In gastric cancer and certain other tumor types, however, the vagus nerve shows the opposite effect [54]. This context-dependence underscores the importance of receptor subtype and cellular milieu in determining functional outcomes.

Sensory nerve fibers—including peptidergic nociceptors expressing transient receptor potential vanilloid 1 (TRPV1), substance P, and calcitonin gene-related peptide (CGRP)—actively participate in tumor biology. Sensory neurons form glutamatergic pseudo-synapses with PDAC cells that drive cancer progression through metabolic reprogramming [20]. In triple-negative breast cancer (TNBC), sensory neurons drive axonogenesis and tumor progression [55], while tumor-derived small extracellular vesicles (sEVs) reprogram sensory nerve identity to promote immunosuppression [56]. At the systemic level, ascending sensory afferents relay tumor-derived signals to the brain, activating a sensory-sympathetic reflex arc that suppresses anti-tumor immunity [27]. These findings implicate sensory neurons in local metabolic coupling, immune modulation, and systemic neuroimmune regulation (Fig. 2, Table 1, Ref. [7,20,26,28,41,52,54,56,57,58,59,60,61,62]).

Table 1. Neural subtypes in the tumor microenvironment: functions, mechanisms, and therapeutic implications.

Neural subtype	Neurotransmitter/ Neuropeptide	Target receptor on tumor/Immune cells	Effects on tumor progression	Effects on tumor immunity	Therapeutic strategies	Evidence level	Key ref(s)
Sympathetic adrenergic	Norepinephrine (NE), Epinephrine	β1-AR, β2-AR, β3-AR, α-ARs	Promotes proliferation, EMT, invasion, metastasis, angiogenesis	Suppresses NK and $CD8^+$ T cytotoxicity; promotes MDSC and M2 polarization; upregulates PD-L1	β-blockers (propranolol), β2-AR antagonists, sympathectomy	Preclinical; clinical (β-blockers, retrospective/Phase II in breast cancer and melanoma)	[7,26,41,57,58]
Parasympathetic cholinergic	Acetylcholine (ACh)	Muscarinic receptors (M1, M3)	Context-dependent	cholinergic anti-inflammatory effects	Vagus nerve stimulation (VNS),	Preclinical	[52,54,59]
Sensory peptidergic	CGRP, Substance P (SP), Glutamate	CALCRL/RAMP1, NK1R, NMDA receptors	Glutamate drives glycolysis via m6A-HK2; SP/CGRP promote invasion	Suppresses NK/T cells; reprograms monocytes; promotes physical ECM barrier via CAFs	Gepants (CGRP antag.), Aprepitant (NK1R antag.), NMDA antagonists	Preclinical	[20,28,56,60,61,62]

Abbreviations: ACh, acetylcholine; α-ARs, alpha-adrenergic receptors; β1-AR, beta-1 adrenergic receptor; β2-AR, beta-2 adrenergic receptor; β3-AR, beta-3 adrenergic receptor; CAF, cancer-associated fibroblast; CALCRL/RAMP1, calcitonin receptor-like receptor/receptor activity-modifying protein 1; CGRP, calcitonin gene-related peptide; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; HNSCC, head and neck squamous cell carcinoma; HK2, hexokinase 2; m6A, N6-methyladenosine; MDSC, myeloid-derived suppressor cell; NE, norepinephrine; NK, natural killer; NK1R, neurokinin 1 receptor; NMDA, N-methyl-D-aspartate; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; SP, substance P; VNS, vagus nerve stimulation.

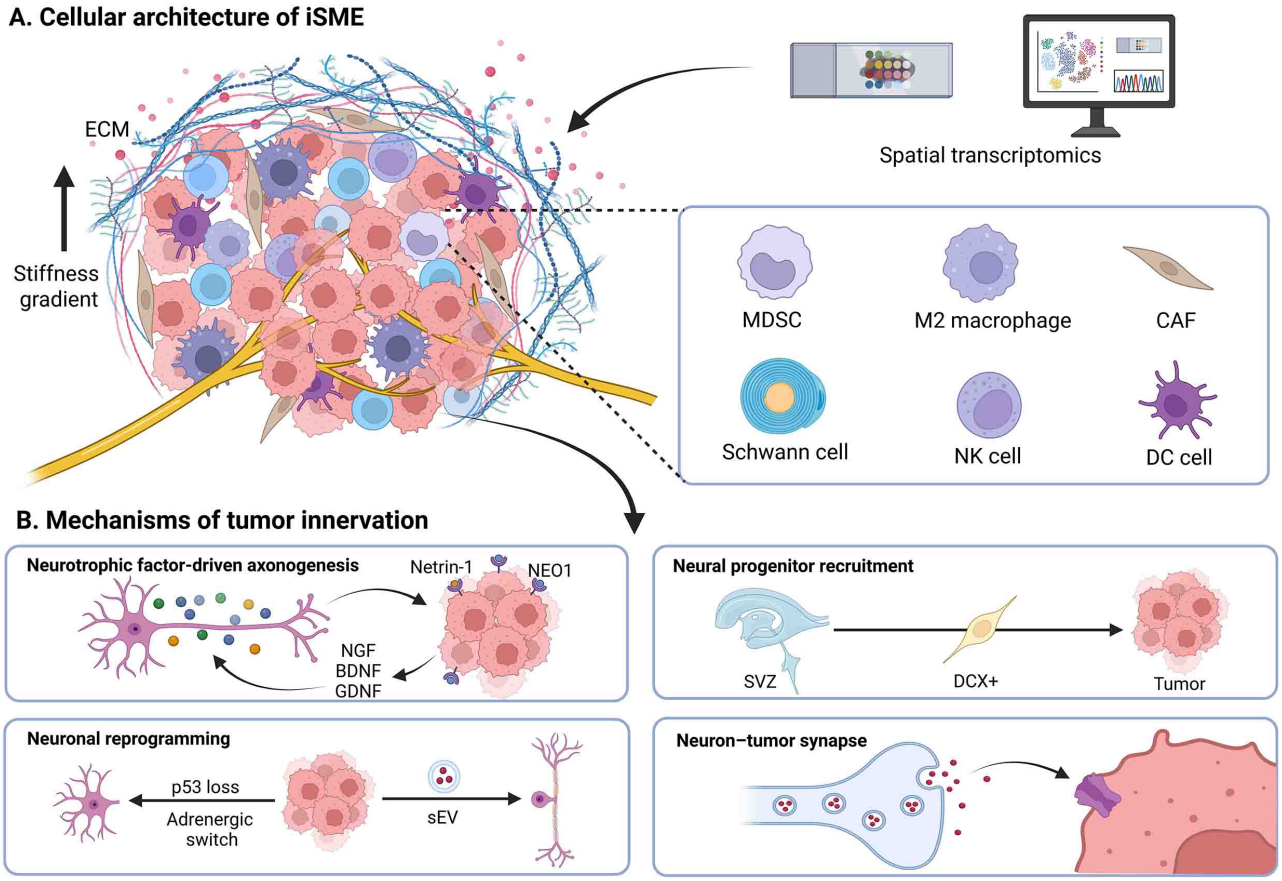

Fig. 3. Mechanisms of tumor innervation and the innervation-specialized microenvironment (iSME). (A) Cellular architecture of the iSME defined by spatial transcriptomics. Nerve fibers are surrounded by distinct niches containing Schwann cells, cancer-associated fibroblasts (CAFs), and immunosuppressive immune cells (MDSCs, M2 macrophages). The ECM exhibits stiffness gradients that dynamically regulate nerve ingrowth. (B) Mechanisms of tumor innervation. (i) Neurotrophic factor-driven axonogenesis (NGF, BDNF, GDNF, Netrin-1/NEO1); (ii) recruitment of neural progenitor cells (DCX+) from the subventricular zone; (iii) cancer-induced neuronal reprogramming (e.g., p53 loss-induced adrenergic switch, and sEV-mediated sensory reprogramming); and (iv) neuron–tumor synapse formation. Abbreviations: BDNF, brain-derived neurotrophic factor; CAF, cancer-associated fibroblast; DC, dendritic cell; DCX, doublecortin; ECM, extracellular matrix; GDNF, glial cell line-derived neurotrophic factor; iSME, innervation-specialized microenvironment; MDSC, myeloid-derived suppressor cell; NEO1, neogenin 1; NGF, nerve growth factor; NK, natural killer; sEV, small extracellular vesicle; SVZ, subventricular zone. This figure was created using BioRender (Jin, M. (2026) https://BioRender.com/4txjj0o).

2.3 The Innervation-Specialized Microenvironment (iSME): Composition and Architecture

The concept of the iSME, first formally articulated in 2020, proposed that nerve fibers within the tumor establish a discrete, spatially organized niche—characterized by specific cellular compositions, signaling gradients, and biophysical properties—that is functionally distinct from other TME compartments [29]. The iSME framework has gained support from subsequent studies of spatially organized neural interactions (Fig. 3).

Spatial transcriptomics applied to PDAC specimens have resolved the cellular subtypes involved in neural invasion, identifying spatially distinct niches organized around nerve fibers [63]. This resolution has been extended to the subcellular level in distal cholangiocarcinoma [64]. These atlases help define nerve-associated tumor niches and identify cellular interactions that merit evaluation as therapeutic targets.

Schwann cells are increasingly recognized as active participants. They supply glutamine to PDAC cells through a Kirsten rat sarcoma viral oncogene homolog (KRAS)/actinin alpha 4 (ACTN4)/p65-NR2A metabolic axis: oncogenic KRAS drives ACTN4 expression, which activates p65 to promote glutamine uptake and conversion to glutamate, the glutamate then activates NR2A on adjacent Schwann cells and is converted back to glutamine, establishing a reciprocal metabolic cycle that fuels perineural invasion [65].

The ECM of the iSME is distinctive in both composition and mechanical properties. Regional differences

in ECM mechanics may influence patterns of nerve invasion [66]. Sympathetic nerve-fibroblast crosstalk [51] and myofibroblast-induced neuroplasticity [67] further establish that the iSME ECM is dynamically maintained through ongoing bidirectional communication. Additionally, immune cell populations within the iSME are enriched for immunosuppressive subsets, and ECM densification induced by sensory neurons in breast cancer creates a physical barrier to immune infiltration [28,63].

Beyond canonical myeloid and lymphoid suppressors, non-neuronal glial cells within the neural niche can themselves be reprogrammed into active immunosuppressive effectors. In glioblastoma, tumor-derived IL-11 instructs astrocytes via STAT3 to upregulate TRAIL, which selectively kills infiltrating T cells and establishes a checkpoint-independent axis of immune evasion [68].

2.4 Neuropeptidergic and Neurotransmitter Signaling in the Neural TME

The chemical language of the neural TME encompasses a rich vocabulary of neurotransmitters, neuropeptides, and metabolites [69]. Catecholaminergic signaling remains the best-characterized axis, mediating immunosuppression through β2-adrenergic receptor (β2-AR) activation, which upregulates programmed death-ligand 1 (PD-L1) and promotes M2 macrophage polarization [41]. Glutamatergic signaling has emerged as a particularly important local pathway: sensory neuron-derived glutamate activates N-methyl-D-aspartate (NMDA) receptors on cancer cells, triggering N6-methyladenosine (m6A) modification of HK2 mRNA and enhancing glycolytic reprogramming [70]. These findings identify glutamatergic signaling as one contributor to metabolic reprogramming in the neural TME.

2.5 Metabolic Coupling and Mitochondrial Transfer in the Neural TME

The discovery that neurons physically transfer mitochondria to cancer cells reveals an additional form of neural–tumor metabolic interaction. Neurons form tunneling nanotubes (TNTs) with cancer cells, through which functional mitochondria are transferred. This establishes a new mechanism by which the nervous system contributes to cancer progression [19].

The transferred mitochondria enhance oxidative phosphorylation (OXPHOS) capacity, providing bioenergetic support for metastatic dissemination. Cancer cells that receive neuronal mitochondria exhibit enhanced invasive capacity and metastatic potential in preclinical models [19]. Beyond organelle transfer, cancer cells exploit neural metabolic resources at multiple levels, including soluble metabolites (serine, glutamate) and signaling molecules [71].

The metabolic dimension of neural-tumor interactions has expanded substantially. Emerging evidence demonstrates that cancer cells co-opt nociceptive nerves to thrive in nutrient-poor environments: under serine starvation, cancer cells exploit nociceptor-derived metabolites to sustain proliferation, revealing a survival mechanism that links neural signaling to metabolic adaptation [72]. This metabolic co-option may also have systemic consequences: neuroimmunometabolic changes in the local tumor niche can coincide with altered immune function elsewhere in the body [73]. The neuropeptidergic dimension of this coupling has been highlighted in recent reviews, which emphasize the diverse repertoire of neuropeptides—CGRP, substance P, VIP, and galanin—that participate in signaling within the neural TME [69].

The KRAS/ACTN4/p65-NR2A axis further exemplifies this metabolic coupling: oncogenic KRAS in PDAC cells drives ACTN4/p65-dependent glutamine uptake and conversion to glutamate, and the resulting glutamate activates NR2A on adjacent Schwann cells and is converted back to glutamine, establishing a reciprocal metabolic cycle that fuels perineural invasion [65]. This establishes a direct mechanistic link between the dominant oncogenic driver of PDAC and the metabolic exploitation of Schwann cells (Fig. 4).

2.6 Synaptic Transmission and Electrophysiological Coupling

The discovery that neurons form functional synaptic connections with cancer cells fundamentally challenges the view of tumors as electrically inert masses. Early work showed that neuronal activity can promote glioma growth through activity-dependent secretion of neuroligin-3 (NLGN3), which activates PI3K-mTOR signaling [18]. Subsequent work established that glioma cells form bona fide glutamatergic synapses with neurons, through which activity-driven calcium transients propagate into the tumor mass, driving proliferation and invasion [12].

Monje has provided a comprehensive overview of the neuroscience of brain cancers, emphasizing that glioma-neuronal interactions represent a continuum from paracrine signaling to bona fide synaptic integration [74].

This coupling is bidirectional: glioma cells can remodel neuronal circuits in ways that reinforce growth-promoting signals [75]. Neuron–cancer synaptic coupling has also been reported outside the CNS. Functional synapses between neurons and small cell lung cancer (SCLC) cells have been reported, driving proliferation through activity-dependent calcium signaling [76]. Aberrant coupling between glutamate receptors and receptor tyrosine kinases enables neuronal control of brain tumor growth [77]. In PDAC, emerging evidence supports the formation of pseudo-synaptic structures that facilitate neuropeptide and neurotransmitter signaling without the full molecular apparatus of a classical synapse [20].

Glutamatergic neurons form functional synapses with SCLC cells, and these synapses are essential for SCLC proliferation [76]. Characterization of the neuronal activity-

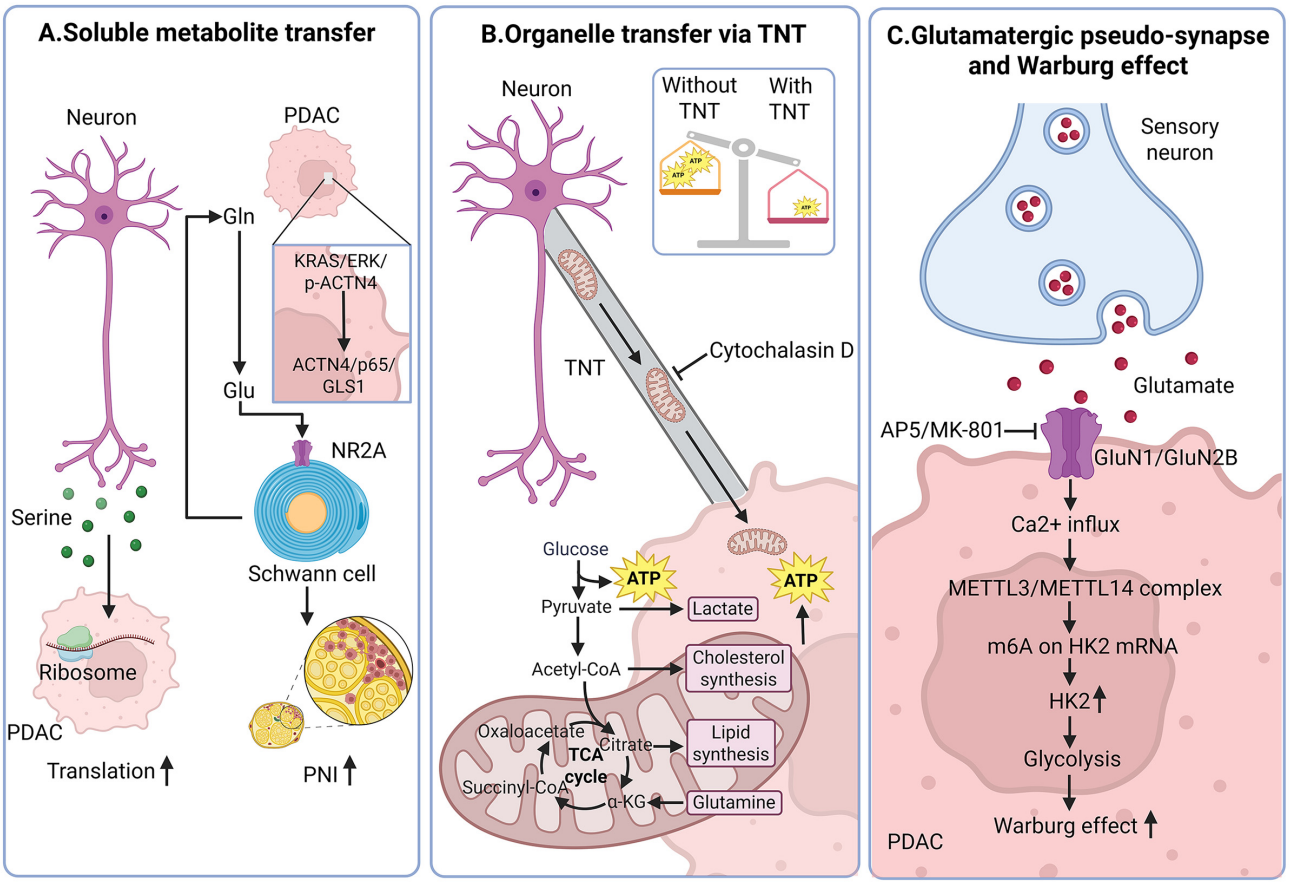

Fig. 4. Metabolic coupling between neurons and cancer cells. Multiple levels at which neural and glial cells supply metabolic resources to cancer cells. (A) Soluble metabolite transfer. Neurons supply serine to support mRNA translation in PDAC cells; Schwann cells supply glutamine to PDAC cells, which convert it to glutamate via KRAS/ACTN4/p65 signaling, and the resulting glutamate activates NR2A on adjacent Schwann cells and is converted back to glutamine, fueling perineural invasion. (B) Organelle transfer via tunneling nanotubes (TNTs). Functional mitochondria are transferred from neurons to cancer cells via TNTs, enhancing oxidative phosphorylation (OXPHOS) and metastatic potential. (C) Glutamatergic pseudo-synaptic coupling. Sensory neuron-derived glutamate activates NMDA receptors, triggering m6A modification of HK2 mRNA, which upregulates HK2 translation and drives the Warburg effect (glycolysis). The convergence of these axes establishes the iSME as an exploitable metabolic niche. Therapeutic opportunities (TNT disruption, glutaminase inhibition, NMDA receptor blockade) are indicated. Abbreviations: ACTN4, actinin alpha 4; AP5, 2-amino-5-phosphonopentanoic acid; ATP, adenosine triphosphate; α-KG, alpha-ketoglutarate; Ca^{2+}, calcium ion; CoA, coenzyme A; ERK, extracellular signal-regulated kinase; Gln, glutamine; GLS1, glutaminase 1; Glu, glutamate; GluN1/GluN2B, NMDA receptor subunits 1/2B; HK2, hexokinase 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; m6A, N6-methyladenosine; METTL3/METTL14, methyltransferase-like 3/14; MK-801, dizocilpine (NMDA receptor antagonist); mRNA, messenger RNA; NR2A, NMDA receptor subunit 2A; p-ACTN4, phosphorylated actinin alpha 4; PDAC, pancreatic ductal adenocarcinoma; PNI, perineural invasion; TCA, tricarboxylic acid; TNT, tunneling nanotube. This figure was created using BioRender (Jin, M. (2026) https://BioRender.com/g2y2iwh).

dependent mechanisms driving SCLC pathogenesis has revealed that calcium influx through synaptic NMDA receptors activates CREB-mediated transcription of pro-proliferative genes [78]. In pancreatic cancer, glutamatergic pseudo-synapses between sensory neurons and PDAC cells have been identified, wherein sensory neuron-derived glutamate activates NMDA receptors on cancer cells, triggering m6A modification of HK2 mRNA and enhancing glycolytic reprogramming [70]. These findings suggest a potential therapeutic strategy: experimental interventions guided by retrograde tracing could target connections within glioblastoma neuron–tumor networks [75]. Broader reviews have synthesized the exploitation of neural signaling pathways in brain metastasis, as well as the diverse mechanisms of neuron-tumor communication in solid tumors—spanning from paracrine signaling to synaptic integration—across cancer types [79,80].

At the epigenetic level, chromatin remodelers such as CHD2 have been shown to regulate the expression of synaptic and axon-guidance genes in pediatric glioma, highlight-

ing a possible transcriptional vulnerability of neuron-tumor networks [81].

2.7 Unresolved Questions and Future Directions for iSME Research

The entangled cellular and molecular relationships at the sensory neuron-cancer interface have been comprehensively characterized, mapping the diverse signaling modalities through which sensory neurons interact with cancer cells and stromal elements [82].

Despite rapid progress, several fundamental questions remain regarding the iSME. Is the iSME a universal feature of solid tumors, or do some cancers remain "neurally cold"? How do the mechanical properties of the iSME dynamically regulate neo-innervation and immune exclusion? Do Schwann cells within the iSME represent a homogeneous population, or do distinct transcriptional states confer different pro-tumorigenic functions? What are the optimal preclinical models—such as orthotopic implants, patient-derived xenografts, or organoid-neuron assemblies—for studying this niche? Addressing these questions will be essential for translating local microenvironmental insights into effective therapies. The local signaling events described here (Pillar I) are also embedded in systemic neural and endocrine networks, which may influence their effects. The next section will address how these local interactions are integrated into whole-body physiological contexts through the lens of ecological therapy (Pillar II) and brain-body crosstalk (Pillar III).

2.8 Triggers of Tumor Innervation: Stress Adaptation as a Unifying Mechanism

A synthesis of the mechanisms described above reveals that tumor innervation can serve as a response to cellular stress. Cancer cells, facing metabolic, proteotoxic, and mechanical stressors within the TME, deploy a conserved repertoire of neurotrophic signals, exosomal cargo, and axon-guidance molecules to recruit neural inputs. These inputs, in turn, provide metabolic substrates (serine, glutamate), bioenergetic support (mitochondrial transfer), and immunomodulatory signals (CGRP, norepinephrine) that alleviate the very stressors that triggered innervation. These mechanisms suggest a possible feedback loop in which stress promotes innervation and neural inputs help tumors tolerate that stress. The clinical implication is that disrupting this loop—whether by blocking neurotrophic signaling, denervating the tumor, or intercepting exosomal communication—may simultaneously address multiple stress-adaptive pathways. Leukemia inhibitory factor (LIF) and galectin-3 (Gal3) have been implicated in neural signaling across several cancer types, suggesting potential shared mediators of tumor innervation [83]. Furthermore, a comprehensive framework has positioned sympathetic, parasympathetic, and sensory nerves as distinct contributors to this stress-adaptive symbiosis [84].

3. Ecological Therapy as a Systems Framework for Cancer Neuroscience

Tumors can exploit chemical, electrical, and mechanical signals within their host environment. The term "ecological therapy" has been proposed for strategies that address these interactions [22]. This second pillar of cancer neuroscience recognizes that the tumor is not a solitary mass, but a dynamic ecosystem shaped by systemic neural, endocrine, and immunological inputs. As such, Pillar II is positioned as an ecological and therapeutic framework: it emphasizes the diffuse, multifactorial nature of tumor–host interactions and the strategies aimed at remodeling these ecological relationships, whereas Section 4 (Pillar III) examines relevant neural circuits in greater mechanistic detail. Consequently, therapeutic strategies must target these systemic ecological relationships rather than merely the tumor cell itself.

3.1 The Tumor as a Neural Ecosystem

The ecological framework conceptualizes the tumor as an evolving ecosystem in which cancer cells, stromal cells, immune cells, neural elements, and the extracellular matrix engage in co-evolving interactions that collectively determine tumor behavior and therapeutic response [85,86]. Within this framework, the iSME may integrate aspects of whole-body physiology, including stress, sleep, exercise, and social behavior, with local molecular programs that influence tumor growth and immune evasion.

The conceptual foundations of tumor ecology draw from decades of work applying ecological and evolutionary theory to cancer. The formalization of cancer as an evolutionary and ecological process established that neoplastic progression can be examined using principles of population dynamics drawn from natural ecosystems [87]. This framework was subsequently extended to demonstrate how adaptive therapy strategies can turn evolutionary principles against the tumor [88], while complementary conceptual updates have emphasized that the TME is not a static backdrop but a dynamically co-evolving community [89]. Within this ecological perspective, neural inputs may exert effects disproportionate to their physical representation within the tumor niche. Neural inputs regulate immune cell trafficking, metabolic resource allocation, and stromal cell behavior, potentially altering the growth capacity of the tumor niche. Moreover, cancer ecosystems are now recognized to operate across multiple scales, from local cellular communities to systemic organ interactions [90].

Ecological therapy seeks to disrupt these sustaining relationships, rather than isolating individual molecular drivers. Tumors exhibit ecological resilience—the capacity to adapt to perturbations through compensatory changes in the microenvironment. Therefore, achieving durable responses may require simultaneously disrupting multiple ecological nodes [86]. The tumor neural ecosystem displays properties analogous to natural ecosystems, includ-

ing niche construction (cancer cells remodel their neural microenvironment for growth), ecological succession (the neural TME evolves as the tumor progresses), and resilience (redundant regulatory mechanisms resist perturbation). These properties have direct therapeutic implications: interventions addressing systemic, local, and circuit-specific mechanisms may warrant testing against single-target approaches.

Surveys have compiled preclinical evidence for denervation strategies across multiple cancer types [91]. Other work has proposed an organ-specific approach to neural targeting based on the role of nerves in gastrointestinal cancer [92].

3.2 Circuit-Specific Ecological Interventions

A major breakthrough in cancer neuroscience has been the identification of specific, anatomically defined neural circuits that control tumor biology. Rather than relying on diffuse autonomic modulation, these discoveries provide a basis for testing more precisely targeted interventions.

3.2.1 Colorectal Cancer Hijacks a Brain-Gut Circuit

Colorectal cancer cells activate a polysynaptic circuit from the lateral septum through the hypothalamus to enteric neurons. This activation sustains tumor growth via altered gut motility, secretion, and immune cell trafficking. Surgical or pharmacological interruption of this circuit at multiple nodes (lateral septum, hypothalamic relay, or enteric targets) successfully suppressed tumor growth, establishing that this malignancy is, in part, a disease of a defined brain–gut circuit [24].

3.2.2 Social Interaction Suppresses Breast Cancer via a Corticoamygdala Pathway

Social housing activates a medial prefrontal cortex–basolateral amygdala (mPFC–BLA) projection that reduces sympathetic outflow to the tumor, decreases norepinephrine release, and enhances natural killer (NK) cell and cytotoxic T lymphocyte (CTL) infiltration [23]. Optogenetic activation of this circuit recapitulated the anti-tumor effects of social interaction, while its inhibition abolished them. In this experimental setting, the finding offers a possible circuit-level explanation for an association between social support and cancer outcomes.

3.2.3 Anxiety Drives Tumor Progression Through a Hypothalamic CRH Circuit

A corticotropin-releasing hormone (CRH) circuit from the basolateral amygdala to the paraventricular nucleus of the hypothalamus (PVN) links anxiety to hypothalamic-pituitary-adrenal (HPA) axis activation and accelerated tumor growth. Chemogenetic inhibition of this circuit suppressed both HPA activation and tumor progression [93].

These preclinical findings support further evaluation of circuit-specific pharmacological, neuromodulatory (e.g., deep brain stimulation or transcranial magnetic stimulation), and behavioral approaches. Whether such approaches improve tumor outcomes or reduce systemic adverse effects in patients remains to be determined.

3.3 Bodywide Ecological Interventions Targeting Systemic Physiology

Systemic physiological states profoundly influence tumor biology through neural and neuroendocrine pathways. Kroemer and colleagues [85] catalogued a comprehensive array of bodywide interventions—including dietary modifications, exercise, sleep optimization, and psychosocial stress reduction—that may influence tumor biology through plausible physiological mechanisms.

Dietary interventions are being investigated as potential ecological interventions. Fasting-mimicking diets, for example, sensitize hormone receptor-positive breast cancer to endocrine therapy by depriving cancer cells of growth factors and glucose [94]. Systematic reviews of dietary modifications have further identified amino acid restriction (methionine, serine, glutamine) as a strategy that exploits the metabolic dependencies created by neural-tumor coupling [95]. Circadian biology provides another dimension: circadian disruption impairs immune function and accelerates tumor growth, whereas chronotherapeutic approaches—timing drug delivery to circadian cycles—can optimize therapeutic efficacy [96]. The ecological perspective also informs immunotherapy design. Drawing on predator-prey theory, the dynamics between immune effectors and cancer prey have been proposed as a critical determinant of immunotherapy outcomes, with direct implications for combination strategies [97]. Furthermore, eradicating metastatic cancer necessitates a deep understanding of the eco-evolutionary dynamics that shape treatment resistance, a realization that has led to the advocacy of adaptive therapeutic strategies—which maintain tumor burden at a controllable level rather than pursuing maximal cytotoxic kill [98].

In experimental and clinical settings, exercise can affect sympathetic tone, circulating catecholamines and cortisol, and NK cell and CTL activity. These effects may counter some immunosuppressive consequences of sympathetic activity in the TME. Sleep patterns can influence adrenergic tone and immune function. In contrast, sleep deprivation can activate the sympathoadrenal axis and impair immune responses. Psychosocial interventions, such as mindfulness-based stress reduction and cognitive-behavioral therapy, may exert their effects through the corticoamygdala and CRH circuits described above [23,93]. Structured group activities could also be studied as supportive interventions, although their effects on tumor-specific neural circuits require validation.

Reviews of the stress–cancer axis describe adrenergic signaling, immune suppression, and angiogenesis and discuss stress reduction as a possible supportive intervention [43].

3.4 Denervation and Autonomic Modulation as Ecosystem Remodeling Strategies

Directly interfering with the neural input to the tumor ecosystem is a powerful therapeutic strategy.

Beta-adrenergic receptor blockade is among the most clinically accessible approaches to inhibiting neural signaling. Propranolol, a non-selective β-blocker, blocks the immunosuppressive, pro-metastatic, and pro-angiogenic effects of adrenergic signaling [57,58]. It enhances anthracycline control of metastasis in triple-negative breast cancer (TNBC) by preventing stress-induced mobilization of myeloid-derived suppressor cells (MDSCs) [58].

Chemical denervation with botulinum toxin type A1 blocks neurotransmitter release from nerve terminals. When combined with anti-PD-1 therapy, it improves antitumor responses in melanoma and colon carcinoma models [99]. Intratumoral botulinum toxin injection is technically feasible, but its oncological efficacy requires clinical evaluation.

Vagus nerve stimulation leverages the parasympathetic pathway, which exerts context-dependent, often tumor-suppressive effects. Indirect cholinergic activation suppresses pancreatic tumor growth via cholinergic anti-inflammatory mechanisms [52,53]. Beyond its local anti-inflammatory effects, the vagus nerve operates as a bidirectional hub at the intersection of brain, body, and tumor, integrating central neuroendocrine states with peripheral immune and metabolic regulation—a multi-faceted dialogue that has been systematically reviewed in the context of cancer [54].

The foundational proof-of-concept for surgical denervation in cancer was established through sympathectomy, which reduces prostate cancer growth and metastasis [7]. Although invasive, this approach has motivated the development of less invasive alternatives, including endoscopic ultrasound-guided celiac plexus neurolysis and focused ultrasound-based neural ablation.

3.5 Integrating Neural Targeting With Immunotherapy and Precision Oncology

The convergence of cancer neuroscience and immuno-oncology provides a rationale for combination therapy. Neural signals suppress anti-tumor immunity through multiple mechanisms: adrenergic suppression of NK cells and T cells [41,57], nociceptor-derived CGRP-mediated immunosuppression [60], and neuropeptide-driven MDSC expansion [100]. Relieving these neural immunosuppressive mechanisms may improve responses to immune checkpoint blockade (ICB) in selected settings.

β-blockade has been shown to synergize with anti-PD-1 antibodies in multiple preclinical breast and lung cancer models [57,58]. Similarly, nociceptor-targeting strategies—such as CGRP receptor antagonists (gepants) or NK1R antagonists (aprepitant)—have shown potential to restore tumor-infiltrating lymphocyte function in experimental models [60,61]. Notably, many of these agents (β-blockers, gepants, aprepitant) are already approved for other indications, supporting investigation of clinical repurposing [57,58].

In summary, the ecological therapy framework reframes cancer treatment as the strategic remodeling of the tumor's systemic and local neural ecosystem (Table 2, Ref. [7,23,52,57,58,59,60,61,85,99,101,102,103,104,105]). While these strategies offer immediate translational promise, their precision relies heavily on understanding the underlying systemic anatomy—the specific brain–body circuits that transmit these regulatory signals. These systemic circuits are examined in the third pillar.

3.6 The Microbiome-Neural Axis in Cancer Ecology

The gut microbiome may link dietary inputs, neural signaling, and immune function in the tumor ecosystem. The microbiome–neural axis operates through multiple channels: microbial metabolites (short-chain fatty acids, tryptophan derivatives) modulate enteric nervous system activity, vagal afferent signaling, and systemic immune tone. Within the tumor context, the intratumoral microbiome influences immunotherapy response by shaping the local immune ecosystem. In this context, bodywide ecological interventions, including microbiome modulation, have emerged as a strategy to reprogram the systemic environment in which tumors evolve [85]. The ecological topology of the gut microbiota has been linked to cancer immunotherapy outcomes, with diverse microbial communities associated with enhanced response to immune checkpoint blockade. The microbiome–neural–immune axis is thus a candidate network through which diet, probiotics, or vagal stimulation might affect tumor behavior. The causal pathways and clinical effects require further study. Furthermore, the concept of cancer as a systemic disease explicitly incorporates the microbiome alongside neural interactions and circadian disruption as core hallmarks of malignancy [38].

4. Brain–Body Crosstalk and Systemic Neural Regulation of Tumor Biology

The conceptual framework of brain-body neural circuitry in tumor pathogenesis provides an integrative lens through which the systemic dimensions of cancer biology can be understood [106]. This third pillar posits that tumors do not merely reside passively within a local tissue niche; instead, they engage in active, bidirectional communication with the central nervous system (CNS), co-opting homeostatic regulatory circuits to promote survival,

Table 2. Clinically actionable ecological therapy strategies in cancer neuroscience.

Strategy	Target/Mechanism	Validated cancer types	Evidence level	Key reference(s)
Propranolol (non-selective β-blocker)	β2-adrenergic receptor (β2-AR) blockade	Breast (TNBC), Melanoma, Lung, Pancreatic, Colorectal	Preclinical	[57,58,102,103,104,105]
Botulinum toxin type A1	Chemical denervation (blocks neurotransmitter release)	Melanoma, Colon carcinoma	Preclinical	[99]
Olcegepant/ Gepants	CGRP-RAMP1 receptor antagonism	Breast, HNSCC	Preclinical	[60,101]
Aprepitant	Substance P NK1R antagonism (extracellular RNA-TLR7 axis)	Breast cancer (metastasis model)	Preclinical	[61]
Muscarinic agonists/VNS	Parasympathetic/Vagal nerve activation	Pancreatic (PDAC), Gastric	Preclinical	[52,59]
Lifestyle interventions	Exercise, Sleep optimization, Psychosocial support	Breast, Colorectal	Epidemiological/ Preclinical circuit validation	[23,85]
Surgical/Chemical sympathectomy	Ablation of sympathetic nerves	Prostate, Pancreatic	Preclinical; Limited clinical (celiac plexus for pain)	[7]

Abbreviations: TNBC, triple-negative breast cancer; HNSCC, head and neck squamous cell carcinoma; RCT, randomized controlled trial; mPFC, medial prefrontal cortex; BLA, basolateral amygdala; VNS, vagus nerve stimulation.

immune evasion, and dissemination. Pillar III examines circuit-level mechanisms. Section 3 (Pillar II) considers their ecological and therapeutic implications. Over the past two years, experimental studies have increasingly tested this model. Several have identified molecular and circuit-level mechanisms through which peripheral tumors communicate with the brain and the brain influences tumor biology [23,27,107,108]. These advances show that neural–tumor interactions may extend well beyond the local tumor niche.

4.1 The Brain as a Systemic Regulator of Tumor Progression

The brain exerts pervasive control over peripheral physiology through three principal axes: the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal (HPA) axis, and the hypothalamic-pituitary-gonadal (HPG) axis. In the context of cancer, tumors can alter these regulatory systems and have been described conceptually as "homeostatic parasites" [106]. Sympathetic outflow promotes a pro-metastatic switch in breast cancer by enhancing EMT and suppressing natural killer (NK) cell cytotoxicity [26]. In contrast, parasympathetic regulation via the vagus nerve exerts context-dependent, often tumor-suppressive effects in pancreatic and gastric cancers [52]. Furthermore, even non-metastatic peripheral tumors can induce significant alterations in hypothalamic neuropeptide signaling, establishing that tumors remodel central neuroendocrine circuits long before overt CNS involvement [25].

Several recent syntheses have comprehensively framed the brain–body interface in cancer. These accounts argue that cancer neuroscience should extend beyond local innervation to encompass the full brain–body interface, where central circuits regulate peripheral tumor biology through autonomic and neuroendocrine channels [109,110]. Bridging brain and body is essential for a complete account of cancer as a systemic disease [111]. Within this framework, the hypothalamus has emerged as a critical hub, where cancer acts as a homeostatic challenge that disrupts the regulation of energy balance, feeding behavior, and neuroendocrine output [25]. Furthermore, foundational insights into neuroimmune interactions have elucidated how central stress responses are translated into peripheral immune modulation [112].

4.2 The Sensory–Sympathetic Reflex Arc: A Paradigm of Systemic Immune Evasion

A recent study identified a vagal sensory–sympathetic pathway through which lung tumors suppress local antitumor immunity in mouse models. Neural tracing, genetic perturbation, and chemogenetic manipulation implicated NPY2R/TRPV1-expressing vagal sensory neurons that innervate lung tumors [27]. These afferents project from the vagal nodose ganglia to the nucleus tractus solitarius in the brainstem; downstream brainstem pathways then increase sympathetic activity. In the lung tumor microenvironment, sympathetic output activates β2-adrenergic signaling in alveolar macrophages, suppressing antitumor T-cell responses. Genetic, pharmacological, or chemogenetic disruption of this pathway enhanced antitumor immunity and reduced lung tumor growth in mice [27]. Furthermore, glioma-neuronal circuit remodeling induces regional im-

munosuppression, wherein active rewiring of local neural circuits creates an immunosuppressive microenvironment in specific brain regions [113].

This vagal sensory–sympathetic pathway links tumor sensing by the brain to local immune regulation in the lung. An important methodological insight from this study is that standard laboratory housing conditions—often maintained at approximately 22 °C, which constitutes a chronic cold stress for mice—can amplify sympathetic tone and thereby confound preclinical assessments of neuro-immune interactions. This observation underscores the necessity of rigorous temperature standardization and careful extrapolation to human physiology [114]. It also underscores the "CNS–PNS–cancer circuit" concept posited by Winkler and colleagues [35], providing mechanistic evidence for this proposed framework. The therapeutic implications of this sensory-sympathetic axis extend beyond mechanistic understanding: its defined anatomy suggests a potential target for cancer immunotherapy, a premise that has been recently articulated as a next-frontier strategy in neuro-oncology [115].

Additional analysis of the same study supports the role of this vagal sensory–sympathetic pathway in lung tumor immunity [27]. Concurrently, the observation that organ-specific sympathetic innervation defines visceral functions provides the anatomical framework for understanding how sympathetic outflow is differentially routed to specific organs and tumor beds [116]. More broadly, the brain-body neural circuitry in tumor pathogenesis has been comprehensively synthesized, mapping the emerging therapeutic frontiers that target these circuits [117]. Finally, the inflammatory reflex—conceptualized as a neural circuit that regulates immune responses through vagal signaling—has been further consolidated into a framework of neuroimmune reflex roles, specifying the afferent, central, and efferent signals that maintain homeostatic immune networks [118,119].

4.3 Psychosocial and Emotional Circuits in Tumor Regulation

The mechanistic link between psychosocial states and cancer outcomes has been investigated through studies of neural circuits that transduce emotional experience into tumor-regulatory biological signals.

In an experimental breast cancer model, social interaction reduced tumor progression through a corticoamygdala circuit. Fiber photometry and chemogenetic manipulation have revealed that social housing activates a medial prefrontal cortex (mPFC) to basolateral amygdala (BLA) projection, which reduces sympathetic outflow to the tumor, decreases norepinephrine release, and enhances NK and CTL infiltration [23]. Conversely, social isolation silences this projection, elevating sympathetic tone and promoting tumor growth.

In another experimental setting, anxiety promotes progression through a discrete CRH-expressing neural circuit in the paraventricular nucleus of the hypothalamus (PVN). Anxiety-induced CRH release activates the HPA axis, leading to glucocorticoid-mediated suppression of tumor-infiltrating lymphocytes [120]. Chemogenetic inhibition of this BLA–PVN–CRH axis attenuated tumor growth even under ongoing anxiogenic stimulation [121].

These findings suggest possible neural mechanisms underlying associations between psychological distress, social support, and cancer outcomes (Fig. 5). Clinical studies are needed to determine whether behavioral interventions targeting these pathways affect tumor outcomes.

4.4 Organ-Specific Neuro-Immune-Metabolic Mechanisms and Systemic Integration

The neural regulation of tumors is not uniform across organs, and accumulating evidence points to organ-specific neuro-immune and metabolic mechanisms. For example, in lung cancer, vagal sensory neurons transmit tumor-derived signals to brainstem nuclei, driving sympathetic efferent activity that suppresses anti-tumor immunity through β2-adrenergic signaling in alveolar macrophages [27]. Sympathetic norepinephrine also inhibits dendritic cell IL-12 secretion and directly suppresses $CD8^+$ T-cell glycolysis and mitochondrial function [122,123]. Similarly, in gastric cancer, vagotomy reverses metabolic reprogramming by suppressing WNT/β-catenin and mTOR signaling [124], whereas in pancreatic cancer, cholinergic signaling through CHRM1 is tumor-suppressive and vagotomy shortens survival [52]. These organ-specific differences underscore context-dependent, tissue-specific neuro-immune and metabolic regulation [73].

These organ-specific mechanisms converge into systemic, multi-organ circuits. Tumors orchestrate a neuroimmune circuit spanning the gut, bone marrow, and spleen to establish whole-body immunosuppression [107], while autonomic β-adrenergic signaling promotes MDSC expansion from the bone marrow and enhances their suppressive capacity [100]. Conversely, the inflammatory reflex—a body-brain circuit that monitors and modulates systemic inflammation through defined neural pathways [119,125]—restrains rather than amplifies immunosuppression, and its dysregulation may permit tumor-driven systemic immune escape [126]. Systemic immunity cannot be understood from the TME alone. Mapping peripheral immune compartments may clarify how neural circuits shape whole-body antitumor responses [127].

4.5 Cancer-Induced Remodeling of the Central Nervous System

Brain–body communication in cancer can be bidirectional. Peripheral tumors exert profound effects on brain function, behavior, and cognition. Tumor-derived inflammatory mediators, including IL-6 and TNF-α, drive neuroinflammation and HPA axis dysfunction [128]. A self-reinforcing brain-body feedback loop in breast cancer pro-

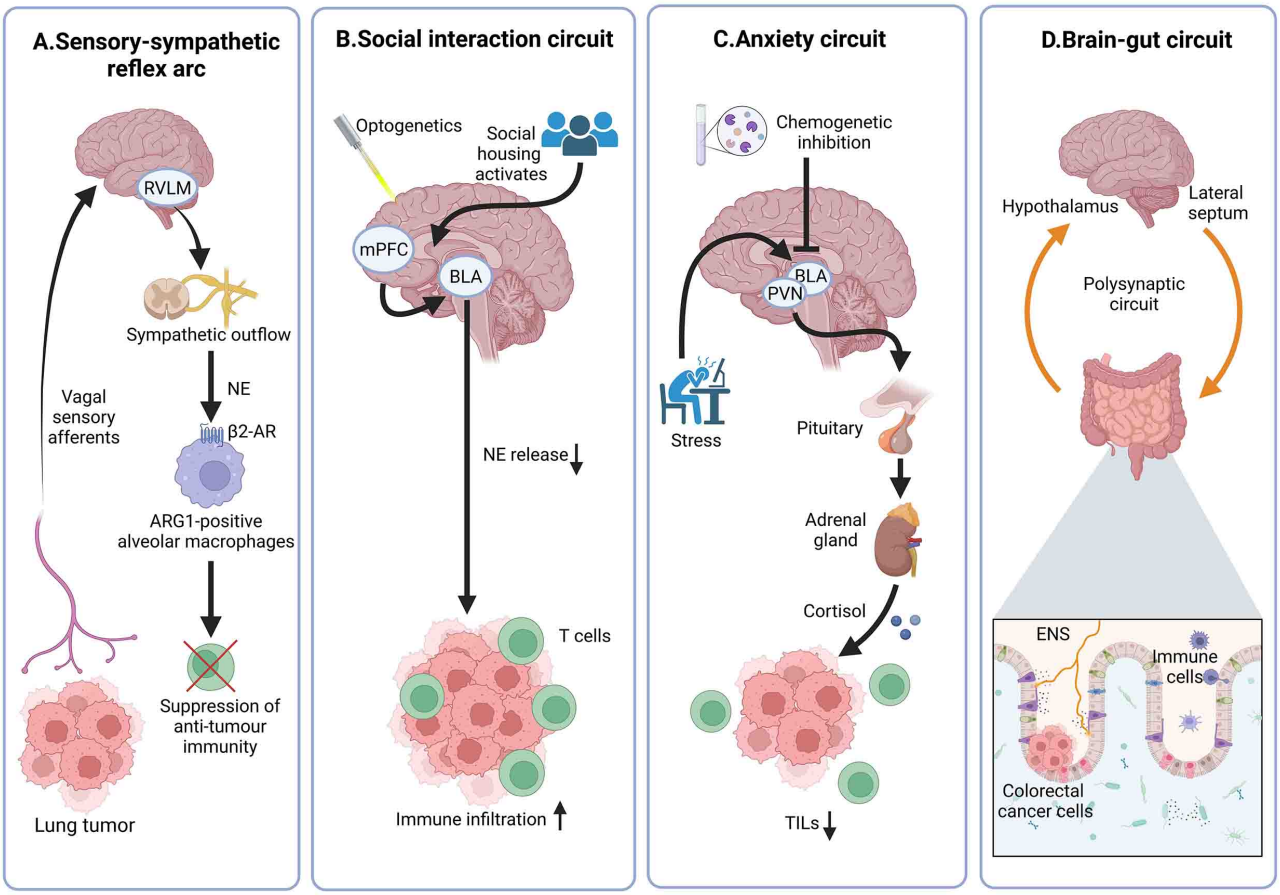

Fig. 5. Brain–body neural circuits regulating tumor progression. Bidirectional communication between peripheral tumors and the central nervous system through anatomically defined circuits. (A) Vagal sensory–sympathetic pathway. Tumor-derived signals activate vagal sensory neurons in the nodose ganglia, which project to the nucleus tractus solitarius and rostral ventrolateral medulla in the brainstem; downstream sympathetic efferent activity in the lung tumor microenvironment activates β2-adrenergic signaling in alveolar macrophages, suppressing antitumor T-cell responses. Interruption of this pathway restores anti-tumor immunity. (B) Social interaction circuit. Social housing activates an mPFC-to-BLA projection, reducing sympathetic outflow and norepinephrine release within the tumor, thereby enhancing immune infiltration. (C) Anxiety circuit. The BLA-to-PVN CRH circuit links anxiety to HPA axis activation and elevated glucocorticoid levels, suppressing tumor-infiltrating lymphocytes (TILs). (D) Brain-gut circuit. Colorectal cancer cells activate a lateral septum-to-enteric polysynaptic circuit to sustain tumor growth via altered gut motility and immunity. These circuits demonstrate that tumor biology is under direct and specific control of defined CNS pathways. Abbreviations: ARG1, arginase 1; β2-AR, beta-2 adrenergic receptor; BLA, basolateral amygdala; CNS, central nervous system; CRH, corticotropin-releasing hormone; ENS, enteric nervous system; mPFC, medial prefrontal cortex; NE, norepinephrine; PVN, paraventricular nucleus of the hypothalamus; RVLM, rostral ventrolateral medulla; TILs, tumor-infiltrating lymphocytes. This figure was created using BioRender (Jin, M. (2026) https://BioRender.com/w8gb690).

gressively amplifies this dysfunction: tumor-derived cytokines act on hypothalamic CRH neurons to sustain HPA activation, leading to glucocorticoid-mediated immunosuppression that, in turn, facilitates further tumor growth, while impairing glucocorticoid negative feedback [129].

Tumor-induced anorexia and cachexia represent another manifestation of tumor-to-brain signaling. Tumor-derived factors such as GDF15 act on hypothalamic appetite-regulating circuits to suppress food intake [130]. Notably, ghrelin-induced NPY expression in hypothalamic neurons promotes brain metastasis tropism in lung cancer patients with low body mass index (BMI), suggesting a mechanistic connection between host metabolic state, central neuroendocrine output, and metastatic organotropism [131].

4.6 Brain Metastasis and the Neuro-Oncological Interface

Breast cancer has been shown to exploit neural signaling pathways for bone-to-meninges metastasis, revealing a mechanism by which cancer cells co-opt existing neural circuits to achieve organ-specific metastatic dissemination [132].

Brain metastasis represents the most direct manifestation of the tumor-brain interface. Recent studies suggest that metastatic cancer cells can exploit neural signaling pathways during CNS dissemination and colonization. The concept of "neural mimicry" describes how metastatic cells adopt gene expression programs resembling neural progenitors, enabling integration into the brain microenvironment and exploitation of neural trophic support [79]. Breast cancer cells have been shown to exploit perineural invasion pathways along cranial and spinal nerve roots to gain access to the leptomeningeal space, mediated by neural guidance molecules [132]. Additionally, the Reelin-LRP8 signaling axis enables breast cancer cells to migrate along the abluminal vascular surface to disseminate widely through the brain parenchyma [133]. These observations point to active, potentially targetable roles for neural guidance signals in CNS metastasis.

These examples show how systemic neural circuits—from vagal sensory–sympathetic signaling to cortical pathways associated with psychosocial states—can influence tumor progression and immune evasion. This systems-level perspective supports a broader view of neural contributions to cancer and provides the anatomical basis for the ecological therapies described in Pillar II. Bridging these mechanistic insights to the clinic, however, requires a pragmatic roadmap for translating neural targeting into precision oncology (Table 3, Ref. [19,20,27,60,61,65,70,71]).

A brain-wide neuronal circuit map in human glioblastoma has helped characterize glioma integration into larger neural networks; tumor position within these networks was associated with patient outcomes [134].

4.7 Interoception, Cachexia, and the Brain-Body Energy Axis

The brain–body interface in cancer extends beyond neural circuits to encompass interoception—the brain's sensing of internal physiological states. A comprehensive framework for brain–body physiology distinguishes local, reflex, and central communication channels that maintain homeostasis [135]. In the cancer context, interoceptive signaling is disrupted: tumors hijack homeostatic circuits to create a self-reinforcing pathological state. Cancer cachexia exemplifies this disruption. It has been defined as a systemic consequence of progressive, unresolved disease, wherein tumor-derived factors act on hypothalamic appetite-regulating circuits to suppress food intake and alter energy expenditure [136]. Area postrema neurons have been identified as critical mediators of interleukin-6 function in cancer cachexia, demonstrating that a specific brainstem structure transduces tumor-derived inflammatory signals into behavioral and metabolic responses [137]. Furthermore, it has been proposed that interoceptive signaling and behavioral biology underlie cachexia, framing it as a disorder of brain–body energy conservation rather than simple weight loss [138]. The cancer–depression comorbidity represents another manifestation of brain–body dysregulation, wherein dysregulated energy homeostasis lies at the crossroads of these conditions, linking brain–body–tumor interactions to the metabolic underpinnings of mood disorders in cancer patients [73]. These findings support further study of how cancer disrupts brain–body homeostasis beyond the local tumor niche.

5. Therapeutic Strategies, Biomarkers, and Precision Neuro-Oncology

The mechanistic advances described in preceding sections suggest several therapeutic approaches, spanning pharmacological targeting, interventional denervation, and neural-immune combination therapies. A recent framework groups neural targeting into nine strategies intended to alter neural–tumor interactions and guide clinical translation [139]. However, the translation of these opportunities into clinical benefit hinges on the validation of robust biomarkers, patient stratification strategies, and rigorous clinical trial designs. This section examines those translational requirements.

5.1 Pharmacological Targeting of Repurposable Neuroactive Agents

The most immediate translational opportunities lie in repurposing existing neuroactive drugs with existing safety data for their approved uses.

β-Adrenergic receptor blockade represents the most clinically advanced strategy. Mechanistic studies have now validated β2-adrenergic receptor (β2-AR) signaling as a driver of SCLC growth, providing a preclinical rationale for testing β-blockers in this neuroendocrine tumor subtype [140]. Retrospective cohort studies have associated non-selective β-blockers such as propranolol with improved outcomes in breast cancer, and preclinical studies have shown that β-blockade synergizes with anthracyclines [58,141,142,143,144], supporting further clinical evaluation.

Given the context-dependent effects of cholinergic signaling in pancreatic cancer, further investigation of parasympathetic signaling as a therapeutic target is warranted.

Neuropeptide receptor antagonism has attracted interest because CGRP receptor antagonists are approved for migraine and NK1R antagonists for antiemetic use. In experimental breast cancer models, CGRP receptor antagonists have reduced tumor growth by blocking CGRP–RAMP1 signaling [101]. Similarly, the substance P NK1R antagonist aprepitant suppresses metastasis by interfering with the extracellular RNA-TLR7 axis [61]. A novel small molecule targeting the transmembrane domain of the p75 neurotrophin receptor has also demonstrated efficacy in impairing melanoma lung invasion [145].

Cholinergic and other neuroactive agents also hold promise. A broader framework has proposed systemati-

Table 3. Key mechanisms of neural–tumor crosstalk: from local signaling to systemic circuits.

Mechanism	Molecular/Cellular players	Validated cancer types	Functional consequence	Therapeutic opportunities	Evidence level	Key ref(s)
Mitochondrial transfer via tunneling nanotubes (TNTs)	Actin-based TNTs, Rho GTPases, Neuronal mitochondria	Breast cancer, Melanoma (preclinical)	Enhances OXPHOS capacity, metabolic flexibility, and metastatic potential	Disrupt TNT formation (actin inhibitors, connexin inhibitors); Mitochondrial fission/fusion blockers	Preclinical	[19,71]
Glutamatergic pseudo-synapses	Sensory neuron-cancer contacts; NMDA receptors; m6A modification of HK2 mRNA	Pancreatic ductal adenocarcinoma (PDAC)	Increases HK2 translation, glycolytic flux (Warburg effect), and proliferation	NMDA receptor antagonists (memantine, ketamine); METTL3 inhibitors (m6A modulation)	Preclinical	[20,70]
Schwann cell-cancer metabolic coupling	KRAS/ACTN4/p65-NR2A axis; Glutamine-to-glutamate conversion	Pancreatic ductal adenocarcinoma (PDAC)	Schwann cells supply glutamine; PDAC-derived glutamate activates Schwann cell NR2A, fueling perineural invasion	Glutaminase inhibitors (CB-839); NR2A receptor blockade	Preclinical	[65]
Sensory-Sympathetic Reflex Arc	Vagal sensory neurons (NPY2R/TRPV1+); nodose ganglia; NTS; sympathetic efferent; alveolar macrophages; β2-AR	Lung cancer (mouse models)	Suppresses antitumor T-cell responses via alveolar macrophage β2-AR signaling; interruption restores immunity	Interruption of vagal sensory–sympathetic pathway; β-blockade; chemogenetic/genetic disruption	Preclinical; clinical (β-blockers)	[27]
Neuropeptide-driven immunosuppression	CGRP-RAMP1; Substance P-NK1R; Extracellular RNA-TLR7 axis	HNSCC, Breast	Reprograms macrophages and MDSCs to immunosuppressive states	Gepants (CGRP antag.); Aprepitant (NK1R antag.)	Preclinical	[60,61]

Abbreviations: ACTN4, actinin alpha 4; β2-AR, beta-2 adrenergic receptor; CGRP, calcitonin gene-related peptide; CTL, cytotoxic T lymphocyte; HNSCC, head and neck squamous cell carcinoma; HK2, hexokinase 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; m6A, N6-methyladenosine; MDSC, myeloid-derived suppressor cell; METTL3, methyltransferase-like 3; NK, natural killer; NK1R, neurokinin 1 receptor; NMDA, N-methyl-D-aspartate; NPY2R, neuropeptide Y receptor Y2; NR2A, NMDA receptor subunit 2A; NTS, nucleus tractus solitarius; OXPHOS, oxidative phosphorylation; PDAC, pancreatic ductal adenocarcinoma; RAMP1, receptor activity-modifying protein 1; TLR7, Toll-like receptor 7; TNT, tunneling nanotube; TRPV1, transient receptor potential vanilloid 1.

cally screening FDA-approved neuroactive compounds—spanning neurotransmitter modulators and ion channel regulators—for anti-cancer activity [22]. The strategic framework for systematically repurposing neuroactive drugs—ranging from β-blockers and neuropeptide receptor antagonists to ion channel modulators—has been comprehensively consolidated, providing a principled roadmap for translating these mechanistically grounded opportunities into clinical oncology [146].

The therapeutic landscape has been comprehensively mapped, with the peripheral neural–tumor microenvironment reviewed as a druggable target, cataloguing preclinical and clinical evidence for neural-targeted interventions [37]. Six strategic therapeutic avenues have been outlined, spanning from neurotransmitter modulation to denervation and neuromodulation [147]. A critical advance is the recognition that clinical trial design must be adapted for cancer neuroscience, incorporating novel approaches featuring neural biomarkers, circuit-specific endpoints, and combination strategies with immunotherapy [148]. Nanodrug approaches have also been investigated. In experimental models, regulation of tumor innervation with nanodrugs improved responses to cancer immunochemotherapy and reduced chemotherapy-induced neuropathic pain [149]. Moreover, systematic screening has identified neuroactive drugs with activity against glioblastoma models, revealing that drugs targeting voltage-gated sodium channels and GABA receptors can disrupt neuron-glioma communication [150]. Finally, the neuro-immune axis represents another source of therapeutic opportunities, bridging mechanistic discoveries to clinical translation [151].

The scope of repurposable neuromodulatory agents has been comprehensively catalogued in recent clinical roadmaps, which organize these agents by neural target class and provide evidence-level summaries across CNS and PNS tumors [32]. As highlighted in these syntheses, the overlap between symptom-directed and tumor-directed effects positions many neuroactive drugs as dual-use candidates, offering a pragmatic framework for accelerating clinical repurposing.

5.2 Interventional Denervation and Neuromodulation

Interventional approaches directly disrupt anatomical neural input to the tumor ecosystem. Surgical sympathectomy provided the foundational proof-of-concept in prostate cancer [7]. To reduce invasiveness, endoscopic ultrasound (EUS)-guided celiac plexus neurolysis—currently used for pain management—has also been investigated for possible effects on PDAC outcomes. Focused ultrasound and stereotactic radiosurgery represent emerging non-invasive modalities for targeted neural ablation. In addition, chemical denervation with botulinum toxin type A1 has improved responses to anti-PD-1 therapy in melanoma models; intratumoral injection is technically feasible [99]. Talin1, a cytoskeletal adaptor protein that facilitates physical contacts between cancer cells and nerve fibers, has been identified as a novel pharmacological target to inhibit perineural invasion [32].

5.3 Integrating Neural Targeting With Immunotherapy

The mechanistic convergence of neuro-immunology and oncology has made combination therapy a priority. The sensory-sympathetic reflex arc provides a powerful rationale: β-AR blockade reverses adrenergic suppression of NK and $CD8^+$ T cells, while simultaneously reducing intratumoral PD-L1 expression [57,58]. Propranolol enhances anthracycline-based immunogenic cell death by suppressing stress-induced MDSC mobilization [58]. Nociceptor-derived CGRP and substance P further represent immunomodulatory targets. Inhibiting CGRP-RAMP1 or NK1R pathways has been shown to restore TIL function and enhance ICB efficacy [60,61]. These preclinical results support designing biomarker-stratified trials of neuromodulators combined with standard immunotherapies.

As underscored in recent analyses of the cancer neuroscience pipeline, the convergence of adrenergic, sensory, and synaptic signaling onto overlapping immune consequences suggests that rational drug combinations—rather than single-pathway inhibition—may be worth testing clinically [32].

5.4 Biomarker Platforms and Precision Neuro-Oncology

A critical barrier to clinical translation is the lack of validated biomarkers to stratify patients who will most benefit from neural-targeted therapies. Recent technological advances are now addressing this gap.

Spatial transcriptomics (e.g., 10x Visium and MERFISH) can characterize cellular and molecular features of the neural tumor microenvironment (nTME) within tissue sections. Combined with imaging and protein-level measurements, it may help assess neural density, nerve subtype composition (including the sympathetic-to-parasympathetic ratio), and activity-related markers [63,64]. High innervation density and a high sympathetic-to-parasympathetic ratio have been associated with poor prognosis in prostate, pancreatic, and gastric cancers [7,40].

Circulating and physiological biomarkers offer non-invasive, dynamic assessment of neuroendocrine tone. Plasma catecholamine levels, heart rate variability (HRV) analysis, salivary cortisol diurnal profiles, and skin conductance can serve as surrogate markers for sympathetic and HPA axis activity [27]. These relatively accessible measures could support longitudinal assessment, but their specificity for tumor-related circuit engagement and therapeutic response must be established.

Dedicated PET tracers targeting neurotrophic, adrenergic, and neuropeptide receptors are under development [152,153,154], and functional imaging modalities such as BOLD/TOLD MRI, EPR oximetry, and hy-

perpolarized 13C-DNP MRI allow real-time assessment of tumor oxygenation, redox status, and metabolism [155,156,157,158,159]. However, these approaches remain largely preclinical and require prospective validation in human cohorts [155,160,161].

AI-driven multimodal integration is being investigated to combine spatial transcriptomic data, clinical imaging, wearable sensor data, and electronic health records to generate predictive algorithms for therapy response. Such integration could contribute to precision neuro-oncology (Fig. 6): the systematic matching of individual patients to circuit-specific or neuropharmacological interventions based on their unique neural regulatory profiles [22,162].

5.5 Limitations, Controversies, and Knowledge Gaps

Despite the conceptual appeal of the three-pillar framework, several limitations must be acknowledged.

First, the field remains disproportionately reliant on preclinical models. Murine peripheral nerve architecture, autonomic ganglion organization, and tumor innervation density differ substantially from humans, and standard laboratory housing at ~22 °C constitutes a chronic cold stress that elevates sympathetic tone and can confound neuro-immune readouts [163]. Humanized models, patient-derived xenografts with co-engrafted neural components, and organoid–neuron assembloids are promising but immature, and species differences in neurotransmitter receptor expression, immune cell composition, and HPA axis regulation further limit extrapolation. Future studies should report housing temperature, account for animal age and sex, and validate key findings in human tissue whenever possible.

Second, it remains unclear whether the three pillars operate uniformly across cancer stages. Neural input may play distinct roles in early tumor initiation—where neoinnervation and stress-adaptive signaling predominate—versus late-stage metastatic colonization, where perineural invasion, mitochondrial transfer, and systemic immune evasion may dominate. For example, in small cell lung cancer, vagotomy suppresses early tumor initiation but is ineffective at later stages, suggesting that vagal innervation contributes primarily to tumor initiation rather than to the maintenance of established tumors [78]. Therapeutic timing should therefore be stage-stratified.

Third, the context-dependence of neural signaling is unresolved: sympathetic activity is pro-tumorigenic in breast, prostate, and small cell lung cancer, whereas parasympathetic/muscarinic signaling can be tumor-suppressive in pancreatic cancer [54].

Fourth, compensatory plasticity after denervation is poorly understood. After pharmacological or surgical denervation, tumors may recover neural inputs through (i) axonal sprouting, regeneration, and reinnervation of denervated tissue, or increased use of alternative neurotrophic receptor pathways (e.g., switching from NGF/TrkA to BDNF/TrkB or GDNF/RET signaling). Other possible compensatory mechanisms include (ii) recruitment of non-neuronal neurotransmitter sources, including Schwann cells, CAFs, and immune cells; (iii) local production of neurotransmitters by cancer cells themselves; and (iv) rewiring of alternative neural circuits. In addition, Schwann cells and resident neural progenitors may support nerve regeneration and reinnervation after denervation, further restoring neuro-tumor crosstalk [164]. These compensatory mechanisms may limit the durability of single-target denervation strategies and argue for combination approaches that simultaneously disrupt multiple nodes—for example, combining β-blockade with CGRP/NK1R antagonism, or pairing denervation with immune checkpoint blockade.

Fifth, baseline human variation and real-world applicability strongly modify the brain–body crosstalk pillar. Chronic systemic stress elevates adrenergic tone and HPA axis activity, potentially amplifying immunosuppression and tumor progression [43]. Metabolic syndrome and obesity alter hypothalamic neuropeptide signaling, systemic inflammation, and vagal tone [165]. Aging is associated with reduced parasympathetic activity, increased sympathetic tone, and impaired immune surveillance [166]. Neurodegenerative diseases may alter central circuit integrity and neuroimmune communication [167]. These factors are largely absent from current preclinical models and may explain heterogeneity in clinical responses to neural-targeted therapies. Future trials should stratify patients by stress burden, metabolic status, age, and neurological comorbidity.

Sixth, blood–brain barrier penetration, systemic neurological side effects, and the lack of validated human biomarkers remain major barriers to translating centrally active neuropharmacological agents into oncology [168,169].

Finally, several discoveries cited here may derive from preprints or early-stage studies [49,55,129]. Independent replication and prospective clinical validation are essential before these findings guide routine practice.

5.6 Future Directions

Several therapeutic directions may address these limitations. Locoregional approaches—including perineural depot injections, intratumoral botulinum toxin, endoscopic ultrasound-guided celiac plexus neurolysis, and ligand-conjugated nanoparticles—could increase local concentrations of neuroactive agents while limiting central exposure and potentially reducing neurological adverse effects [32,146,170]. Nanoparticles functionalized with nerve-targeting ligands (e.g., against neurotrophic receptors or axon-guidance molecules) offer a promising route for selective delivery to tumor-innervating fibers, potentially reducing off-target central effects [171,172]. For agents requiring CNS access, receptor-mediated transcytosis, BBB-penetrant small molecules, and focused ultrasound offer complementary routes across the BBB/BBTB

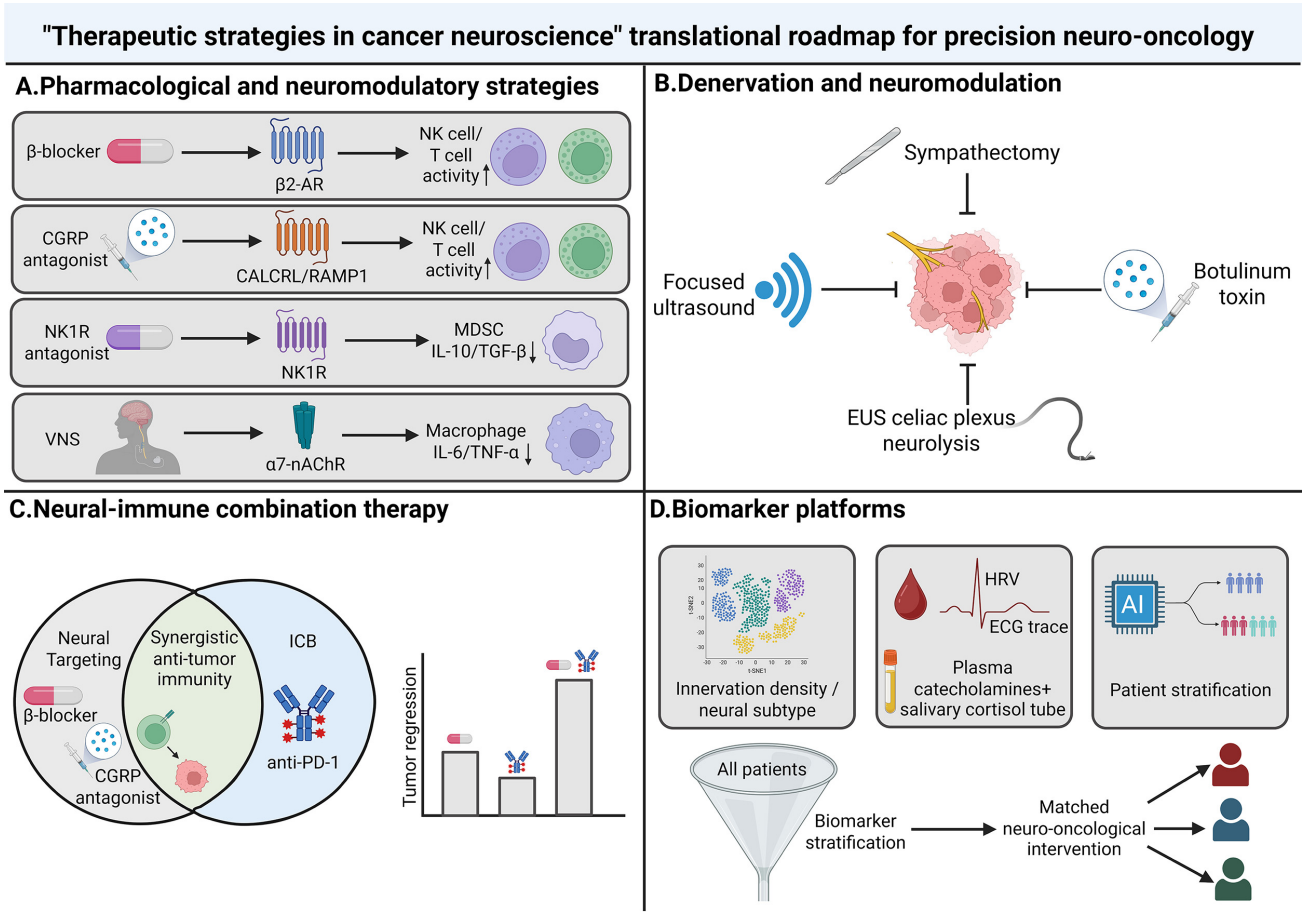

Fig. 6. Therapeutic strategies and precision neuro-oncology. Translational roadmap from mechanistic discovery to clinical application. (A) Pharmacological and neuromodulatory strategies. Clinically actionable agents targeting adrenergic receptors (propranolol), the CGRP-RAMP1 axis (gepants), the substance P-NK1R axis (aprepitant), and cholinergic pathways (vagus nerve stimulation). (B) Denervation and neuromodulation. Surgical sympathectomy, chemical denervation (botulinum toxin), endoscopic ultrasound-guided celiac plexus neurolysis, and focused ultrasound. (C) Neural-immune combination therapy. Synergy between β-blockers/CGRP antagonists and immune checkpoint blockade (anti-PD-1/PD-L1) to relieve neural-mediated immunosuppression. (D) Biomarker platforms for precision neuro-oncology. Integration of spatial transcriptomics (innervation density/neural subtypes), circulating biomarkers (plasma catecholamines, salivary cortisol, heart rate variability), and AI-driven multi-modal data to match patients to neuro-oncological interventions. Abbreviations: α7-nAChR, alpha-7 nicotinic acetylcholine receptor; AI, artificial intelligence; β2-AR, beta-2 adrenergic receptor; CALCRL/RAMP1, calcitonin receptor-like receptor/receptor activity-modifying protein 1; CGRP, calcitonin gene-related peptide; ECG, electrocardiogram; EUS, endoscopic ultrasound; HRV, heart rate variability; ICB, immune checkpoint blockade; IL-6, interleukin-6; IL-10, interleukin-10; MDSC, myeloid-derived suppressor cell; NK1R, neurokinin 1 receptor; PD-1, programmed cell death protein 1; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; VNS, vagus nerve stimulation. This figure was created using BioRender (Jin, M. (2026) https://BioRender.com/846ubg7).

[173,174,175]. Non-pharmacological neuromodulation, such as vagus nerve stimulation, provides additional circuit-specific options with reduced systemic neurotoxicity [176]. Moving forward, the convergence of spatial multi-omics, AI-driven biomarker discovery, and precision neuromodulation platforms may improve translational research. The three-pillar framework—iSME, ecological therapy, and brain–body circuitry—provides a structure for this work. For example, spatially resolved metabolomics could be integrated with real-time *in vivo* calcium imaging in awake, tumor-bearing mice. This approach could reveal changes in neural–tumor metabolic coupling during stress or social interaction. Bridging these local interrogations to human physiology, non-invasive brain–body mapping—combining functional MRI with wearable biosensors—offers a longitudinal window into the engagement of defined sensory–sympathetic and corticolimbic circuits in patients. Combining multiscale imaging, single-cell spatial omics, and causal inference methods could move the field toward more predictive interventions. Whether neuro-oncological treatments can be adapted to an individual's changing neural–immune state remains to be tested.

6. Conclusions

Cancer neuroscience has undergone a profound transformation over the past decade, evolving from mechanistic obscurity into a rigorously grounded discipline. The field is now organized around three conceptual pillars: the iSME, where nerves directly regulate local cancer behavior and immune function; ecological therapy, which aims to remodel the systemic neural and stromal ecosystem; and brain-body neural circuitry, which positions tumors as active participants in bidirectional, systemic neuroendocrine communication.

Cancer neuroscience offers an emerging framework for therapy, integrating neural, immune, and metabolic dimensions into a unified therapeutic framework [22]. The neuro-immune axis, in particular, constitutes a key source of therapeutic opportunities that bridge mechanistic discoveries to clinical translation [151].

The past two years have witnessed landmark breakthroughs across all three pillars, including identification of a vagal sensory–sympathetic pathway that suppresses antitumor immunity in experimental lung cancer [27]. These advances show that neural mechanisms can influence cancer beyond the local tumor niche. The transition from bench to bedside now requires a concerted effort to validate neural biomarkers, standardize neuro-immune combination protocols, and advance precision neuro-oncology. By integrating the local niche, the systemic circuit, and the ecological context, the three-pillar framework offers a conceptual guide for future cancer neuroscience research and therapeutic development.

The recognition that cancer is a systemic disease, involving neural interactions, circadian disruption, and microbiome-related mechanisms, has further catalyzed the field [38]. The most recent comprehensive assessment traces the arc from foundational discoveries to current translational frontiers, providing a roadmap for the next decade [35]. Crucially, cancer ecosystems operate as dynamic interplays across scales—from local cellular communities to systemic organ interactions—suggesting a need to evaluate therapies across these scales [90]. Ultimately, the convergence of cancer neuroscience with ecological theory, brain-body physiology, and precision oncology could eventually support neural-targeted interventions that complement established treatments and address systemic influences on malignancy.

Author Contributions

HRD: Writing – original draft, Visualization. MZJ: Conceptualization, Writing – original draft, Writing – review & editing. WLJ: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used an AI-assisted writing tool (Biomni, Phylo) for language polishing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the publication.

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