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Review Article

The Brain–tumor axis: Tumor pathogenesis and therapeutic strategies from a cancer neuroscience perspective

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ABSTRACT

Cancer research has undergone a fundamental paradigm shift, moving beyond a tumor-cell-centric framework toward a systems-level understanding in which the nervous system occupies a central regulatory role. The brain and its peripheral extensions engage in sophisticated, bidirectional crosstalk with tumors across multiple biological scales. This complex relationship, now termed the brain-tumor axis, operates through mechanisms spanning systemic neuroendocrine regulation, local neural-tumor interactions, and the distinctive biology of the central nervous system as both a primary and metastatic tumor site.

At the systemic level, the brain modulates distant tumors via stress-responsive neuroendocrine pathways and discrete central-peripheral neural circuits that govern catecholaminergic innervation and antitumor immune surveillance. Neuropeptide systems further serve as integrative messengers within this axis, acting via G protein–coupled receptors on malignant, stromal and immune cells to orchestrate proliferation, stromal remodeling and immune polarization. Within the tumor microenvironment, neural-tumor interactions encompass perineural invasion, Schwann-cell-mediated pro-tumorigenic reprogramming, and neural remodeling of the immune landscape. In primary brain tumors, malignant cells integrate into host neural circuits and exploit glial plasticity to sustain proliferation and immune evasion. For metastatic disease, circulating tumor cells breach the blood–brain barrier and adapt to the brain parenchyma through dynamic interactions with resident astrocytes and microglia.

We further discuss the remote consequences of tumors on nervous-system homeostasis, including cancer-induced pain, cognitive impairment, and cachexia, and survey emerging therapeutic strategies targeting this axis, from β-adrenergic blockade and neurotrophic signaling inhibition to physical neuromodulation. We propose that the brain–tumor axis represents an emerging integrative hallmark of cancer, defined by the context-dependent duality of neural signaling, whereby identical pathways elicit opposing pro- or anti-tumorigenic effects contingent on tumor type, disease stage, and microenvironmental context. Collectively, these insights position cancer neuroscience as a transformative frontier in precision oncology and signal a conceptual transition toward brain–tumor-axis-based treatment paradigms.

1. Introduction

Cancer research is undergoing a profound paradigm shift, moving from a tumor-cell-centric focus on genetic and epigenetic alterations toward a systems-level conception in which tumors are regarded as complex ecosystems engaged in dynamic, reciprocal interactions with the host [1,2]. Within this framework, the nervous system—the highest-order regulatory network of the body—has emerged as a critical participant in tumor initiation, metastasis and therapeutic resistance, catalyzing the rise of cancer neuroscience as an interdisciplinary frontier [1,3]. Long regarded as a passive bystander to tumor invasion, the nervous system is now recognized to engage in sophisticated bidirectional crosstalk with tumors across both central and peripheral compartments [4–6]. The brain remotely modulates peripheral tumor behavior through central–peripheral neural circuits, neuroendocrine networks and neuroimmune interactions [2,6], whereas tumors, in

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turn, actively remodel, co-opt and even mimic neural structures and functions to drive their own proliferation and dissemination, while concurrently perturbing nervous-system homeostasis [1,5,7]. These interactions pervade virtually every core dimension of tumor biology, spanning initiation, angiogenesis and metabolic reprogramming through to immune evasion, therapeutic failure and distant metastasis [3,8,9]. Deciphering the molecular logic and regulatory architecture of the brain–tumor axis not only refines our conception of cancer as a systemic disease but also opens new therapeutic avenues directed at the neural–tumor dialogue [4,8]. In this review, we advance a unifying thesis: the brain–tumor axis constitutes an emerging integrative hallmark of cancer, defined by the context-dependent duality of neural signaling. Identical pathways, ranging from parasympathetic acetylcholine to glutamatergic transmission, can exert diametrically opposing effects depending on the biological context. This duality raises the central question of the field: which molecular rheostats govern such functional polarity, and how might they be therapeutically exploited? Here, we review recent advances in this area, focusing on the systemic regulation of tumors by the brain, local neural interactions within the tumor microenvironment, the distinctive role of the brain as a site of both primary and metastatic disease, and emerging therapeutic strategies targeting this axis. Our aim is to provide a foundation for future mechanistic investigation and clinical translation. (Fig. 1).

2. Brain regulation of tumors: central–peripheral neural circuits in tumor initiation and progression

2.1. Psychological stress and the neuroendocrine–immune network

As the principal integrative center of the stress response, the brain modulates systemic physiology through neuroendocrine and autonomic pathways that directly shape cancer progression. Chronic psychological stress is an established driver of tumor evolution [10], acting primarily through sustained activation of two canonical stress axes: the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) [6,10]. HPA axis activation drives persistent glucocorticoid (cortisol) secretion, while SNS excitation elevates circulating catecholamines (epinephrine and norepinephrine). Collectively, these stress hormones impair immune surveillance by suppressing cytotoxic lymphocyte activity and expanding immunosuppressive cell populations, thereby enhancing tumor immune evasion and metastatic potential [10]. In breast cancer survivors, heightened amygdalar reactivity to social threat correlates positively with both perceived stress and elevated peripheral C-reactive protein, implicating a direct neural link between central emotional processing and peripheral inflammation in the oncological context [11].

Recent studies have delineated the discrete neural circuits mediating these effects. In murine breast cancer models, tumor burden itself functions as a chronic stressor, inducing anxiety-like behavior and activating corticotropin-releasing hormone (CRH)-expressing neurons in the central medial amygdala (CeM). These neurons potentiate intratumoral sympathetic tone and norepinephrine release via a polysynaptic CeMˆCRHˆ → lateral paragigantocellular nucleus (LPGi) pathway, thereby attenuating antitumor immunity and accelerating tumor growth [12]. Conversely, prosocial behavior engages a glutamatergic projection from the anterior cingulate cortex (ACC) to the basolateral amygdala (BLA), which suppresses intratumoral sympathetic activity and confers antitumor effects [13]. Furthermore, psychological stress drives SNS-mediated norepinephrine signaling that downregulates the RNA demethylase ALKBH5 in pancreatic ductal adenocarcinoma (PDAC) cells. Loss of ALKBH5 generates aberrant N^6-methyladenosine (m^6A) modifications on cancer-cell transcripts, notably on pro-neurogenic mRNAs. YTHDF family readers (YTHDF1/2/3) recognize these m^6A motifs and recruit RNA-binding proteins together with the endosomal sorting complex required for transport (ESCRT) machinery, thereby directing the modified transcripts into extracellular vesicles [14,15].

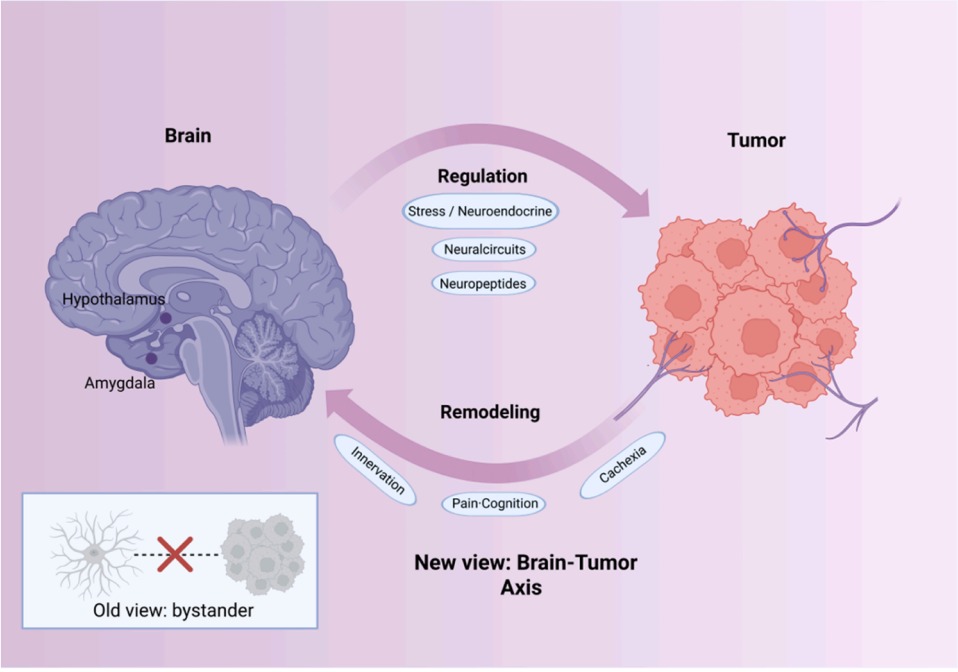


Fig. 1. The brain–tumor axis: a new paradigm. The nervous system and tumors engage in reciprocal crosstalk across multiple biological scales. Systemically, the brain governs distant tumors through stress-responsive neuroendocrine pathways and central–peripheral neural circuits that shape catecholaminergic innervation and antitumor immunity. Within the tumor microenvironment, local interactions include perineural invasion, Schwann-cell-mediated pro-tumorigenic reprogramming, and neural remodeling of the immune landscape. In primary brain tumors, malignant cells integrate into host neural circuits and exploit glial plasticity to sustain proliferation and immune evasion, whereas metastatic cells breach the blood–brain barrier and adapt to the parenchyma through dynamic interactions with astrocytes and microglia. Reciprocally, tumors perturb nervous-system homeostasis, producing remote manifestations such as cancer-related pain, cognitive impairment, and cachexia. Together, these interactions establish cancer neuroscience as a foundation for brain–tumor-axis–based therapeutic paradigms.

The m⁶A-binding protein hnRNPA2B1 adds a further layer of control, governing the sumoylation-dependent loading of these transcripts into exosomes through ceramide-dependent pathways [16]. Pro-neurogenic transcripts are thus preferentially exported, whereas housekeeping RNAs are retained within the cell. Upon delivery to tumor-resident neurons, the m⁶A-modified RNAs drive pathological innervation and malignant progression [17]. Taken together, these findings establish a mechanistic neurobiological framework for stress-driven tumor promotion and highlight the central role of brain emotion- and stress-regulatory circuits in the systemic governance of cancer (Fig. 2).

Although these discrete neural circuits have been characterized largely in murine models, a growing body of clinical evidence supports the functional conservation of stress-regulatory and emotional circuits in patients with cancer. Limbic structures, including the amygdala, hippocampus, prefrontal cortex, and hypothalamus, display conserved anatomical organization and connectivity across mammals, with homologous nuclei serving comparable roles in stress integration and autonomic output. Neuroimaging of cancer survivors reveals structural and functional alterations in these regions that track with disease progression, treatment resistance, and inflammatory biomarkers [18]. Clinical trials of β-adrenergic blockade and psychosocial interventions further demonstrate measurable effects on tumor biology and patient outcomes, indirectly confirming the conservation of these central–peripheral pathways [19,20]. Retrospective analyses, for example, link β-blocker use to improved survival across multiple tumor types, while prospective trials of stress-reduction interventions report lower pro-inflammatory cytokine levels and enhanced immune function. Definitive mapping of the human neural circuits that govern tumor progression nonetheless remains technically demanding, constrained by the invasiveness of circuit-tracing techniques and by ethical considerations, and stands as a priority for translational cancer neuroscience. Non-invasive approaches such as high-resolution functional MRI, magnetoencephalography, and peripheral autonomic biomarkers offer a promising route to bridging this gap.

2.2. *Remodeling of peripheral nerves in the tumor microenvironment*

Contrary to early assumptions, the tumor microenvironment is no 'neural desert'. Many solid tumors are densely innervated both within and at their margins, a phenomenon termed tumor innervation. Tumors actively induce axonogenesis and neurogenesis, processes collectively designated cancer-associated neurogenesis [21,22]. The nervous system therefore constitutes an active, integral component of the tumor microenvironment, participating in and driving malignant behavior throughout disease progression [5,23]. To recruit and direct nerve fiber ingrowth, tumor cells secrete an array of neurotrophic factors —

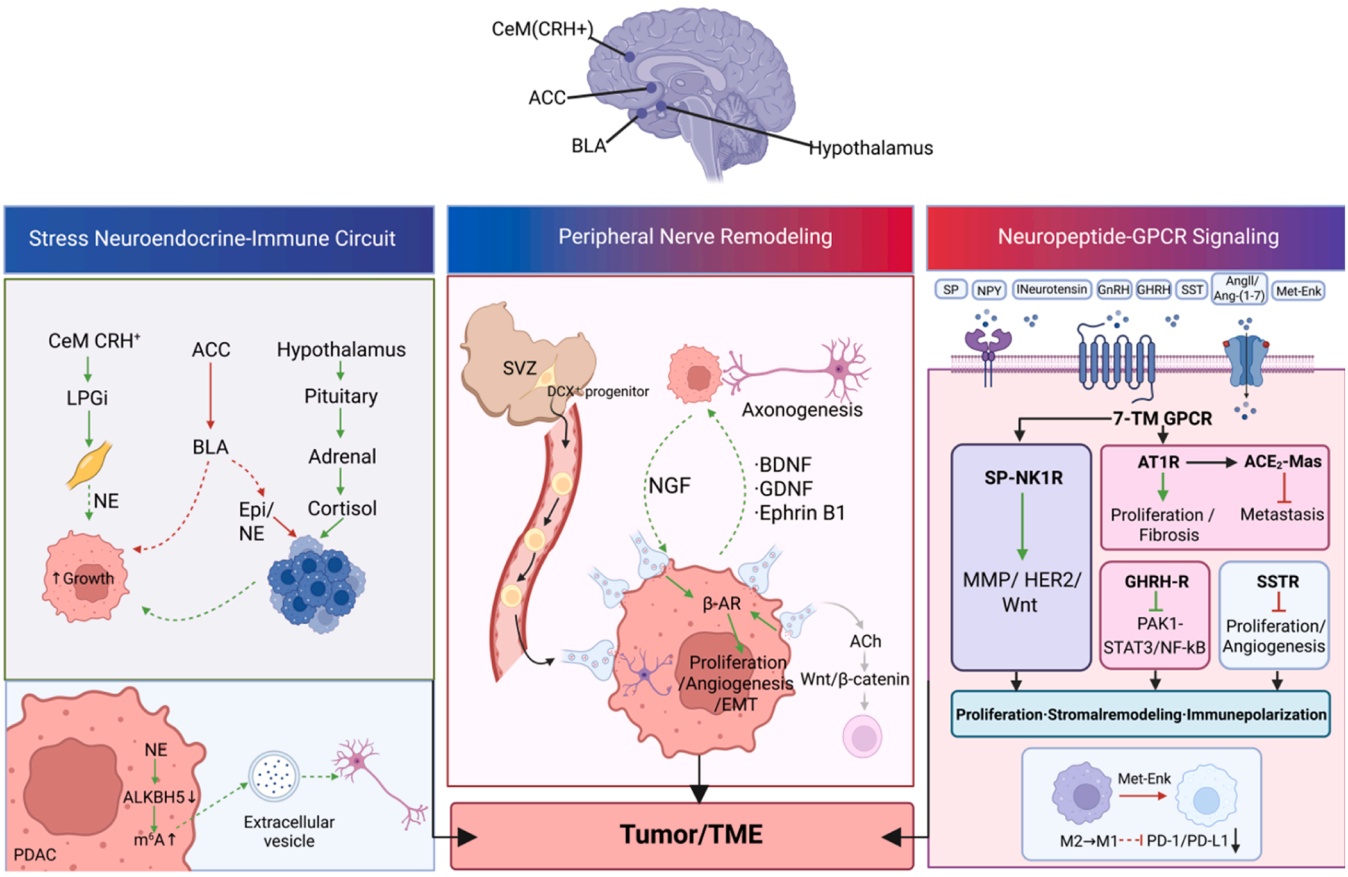


Fig. 2. Brain regulation of peripheral tumors through neural circuits, neuroendocrine signaling, and neuropeptide systems. The brain governs distant tumors along three routes. Green arrows denote pro-tumorigenic interactions, red arrows anti-tumorigenic interactions, and gray dashed arrows context-dependent signaling. **(1)** Stress neuroendocrine–immune circuit: chronic stress activates the HPA axis and sympathetic nervous system (SNS), raising glucocorticoids and catecholamines that suppress cytotoxic lymphocytes and favor immune evasion. CRH neurons in the central medial amygdala (CeM) raise sympathetic tone via a CeMˆCRHˆ→LPGi pathway, whereas an ACC→basolateral amygdala projection is antitumorigenic. In PDAC, SNS-derived norepinephrine downregulates ALKBH5, generating m⁶A transcripts that reach tumor-resident neurons through extracellular vesicles to drive innervation. **(2)** Peripheral nerve remodeling: tumor-secreted NGF, BDNF, GDNF, and ephrin-B1 induce axonogenesis; the resulting fibers signal through β-adrenergic receptors (proliferation, angiogenesis, EMT), while acetylcholine–Wnt/β-catenin signaling acts context-dependently. **(3)** Neuropeptide–GPCR signaling: neuropeptides act through GPCRs to drive proliferation, stromal remodeling, and immune polarization, with antagonism often encoded within one family—the pro-tumorigenic AT1R arm versus the tumor-restraining ACE_2–Mas arm.

including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF) — alongside axon-guidance molecules such as Ephrin B1 [21].

Once established within the tumor, newly formed nerve fibers engage in bidirectional crosstalk with tumor and stromal cells via neurotransmitters and neuropeptides, profoundly reshaping tumor biology. Sympathetically derived norepinephrine activates β-adrenergic receptors to promote tumor-cell proliferation, angiogenesis, and epithelial-mesenchymal transition (EMT) [21,24]. Parasympathetic innervation exerts context-dependent effects. In gastric and prostate cancers, acetylcholine expands the cancer stem-cell pool via Wnt/β-catenin activation [21] and promotes immunosuppression through the vagal–ABHD16A–LysoPS–ILC3–IL-22–PD-L1 axis [25]. In early-stage pancreatic ductal adenocarcinoma (PDAC), by contrast, parasympathetic denervation accelerates tumor growth [26,27], indicating that acetylcholine curbs inflammation and restrains stromal fibrosis [28]. In androgen-deprived prostate cancer, muscarinic signaling preserves cellular differentiation and suppresses neuroendocrine transdifferentiation [29]. his functional polarity is dictated by receptor subtype (M1–M5), disease stage, and tumor genotype, including TP53, KRAS, and AR status [26–29]. Beyond local nerve remodeling, tumors can also co-opt the regenerative capacity of the nervous system at a distance. Philippe Mauffrey and colleagues demonstrated that prostate cancer induces doublecortin (DCX)-expressing neural progenitor cells to emigrate from the subventricular zone, enter the systemic circulation, home to the tumor, and differentiate in situ into adrenergic neurons that directly drive tumor growth and metastasis [30]. Tumor cells can further subvert neural differentiation programs intrinsically: in head and neck squamous cell carcinoma, p53 loss reprograms tumor-associated sensory neurons toward an adrenergic phenotype, and these reprogrammed neurons in turn promote disease progression [31]. Evidence additionally indicates that, under certain conditions, tumor-resident macrophages can acquire neuron-like properties, further expanding the cellular complexity of tumor innervation [23]. Collectively, these findings delineate a dynamic landscape in which tumors actively recruit, remodel, and de novo generate neural components, exploiting their signaling to fuel malignant progression (Fig. 2).

2.3. *Neuropeptide systems in tumor progression and remodeling of the immune microenvironment*

Beyond classical neurotransmitters, neuropeptides are a structurally diverse class of signaling molecules through which the nervous system imposes long-range, receptor-mediated control over tumor biology. Acting predominantly via G protein–coupled receptors (GPCRs) on malignant, stromal and immune cells, they integrate systemic neuroendocrine inputs with local remodeling of the tumor microenvironment, emerging as central nodes in cancer neuroscience [32] (Fig. 2).

The renin–angiotensin system exemplifies this paradigm through two antagonistic axes. The canonical ACE–angiotensin II–AT1R axis drives proliferation, angiogenesis, EMT and stromal fibrosis, with AT1R overexpression predicting poor prognosis and therapeutic resistance [33]. Conversely, downregulation of the ACE2–Ang-(1-7)–Mas axis activates store-operated calcium entry and PAK1/NF-κB/Snail1 signaling, suppresses E-cadherin and drives breast cancer metastasis [34], whereas ACE2 activity identifies immuno-hot tumors and Ang-(1-7) sensitizes breast tumors to chemotherapy and immune checkpoint blockade [35].

The tachykinin family represents a second pro-tumorigenic network. Substance P (SP)–NK1R signaling promotes breast cancer migration through MMP-2/MMP-14 upregulation [36], transactivates HER2 and EGFR via c-Src– and metalloproteinase-dependent mechanisms, and engages AKT/mTOR and Wnt/β-catenin cascades [37]. The clinically approved NK1R antagonist aprepitant suppresses Wnt and mTOR signaling in colon cancer, hepatoblastoma and glioblastoma [38], while SP polarizes macrophages towards an M2-like phenotype via heme oxygenase-1 (HO-1) induction [39]. The immune-cell-restricted tachykinin hemokinin-1 acts preferentially through NK1R, mediating inflammation and immune regulation within the tumor microenvironment [40].

Hypothalamic–pituitary peptides constitute further tractable nodes. Gonadotropin-releasing hormone (GnRH) analogs exert direct antitumor effects on GnRH-R-positive tumors and have been formulated as receptor-targeted nanoparticles for ovarian, breast and prostate cancers [41]. Growth hormone-releasing hormone (GHRH) receptor antagonists such as MIA-602 downregulate the PAK1–STAT3/NF-κB inflammatory axis to suppress gastric cancer growth [42]. Somatostatin analogs elicit antiproliferative and antiangiogenic effects through SSTR-coupled cascades; in radiolabeled form they underpin peptide receptor radionuclide therapy, with indications extending beyond gastroenteropancreatic neuroendocrine tumors to pulmonary carcinoids, paragangliomas and meningiomas [43].

Additional neuropeptide systems contribute through distinct mechanisms. Neuropeptide Y promotes proliferation and angiogenesis, with hypoxia-induced Y2R/Y5R upregulation and DPPIV-mediated cleavage to NPY3–36 amplifying pro-tumor actions in pediatric and gastrointestinal cancers [44]. Neurotensin–NTSR1 (also termed NTR1) co-expression activates Wnt/β-catenin signaling, driving EMT and metastasis in hepatocellular carcinoma [45]. Methionine enkephalin reprograms macrophages from M2 to M1, suppresses MDSCs and expands effector T cells while attenuating PD-1/PD-L1 expression, enhancing antitumor immunity in colorectal cancer [46].

Functional antagonism is often encoded within a single neuropeptide family rather than between families: within the renin–angiotensin system, the Ang II–AT1R and Ang-(1-7)–Mas arms produce opposing effects [33–35], as do distinct opioidergic signals [46]. Non-selective targeting therefore risks neutralizing the beneficial arm, which makes subtype selectivity essential. From a translational standpoint, the SSTR and NK1R axes stand out as priority nodes, having reached clinical validation through radionuclide therapy [43] and aprepitant [38], respectively. Neurotensin and hemokinin-1, by comparison, remain largely correlative and await confirmation in immunocompetent models. Collectively, neuropeptide systems function as integrative messengers within the brain–tumor axis, orchestrating proliferation, stromal remodeling and immune polarization. The pharmacological tractability of their cognate GPCRs, combined with the clinical maturity of established neuroendocrine agents, marks this network as a compelling frontier for drug repurposing in precision oncology (Table 1). However, translating these receptors into routine clinical biomarkers presents distinct challenges.

Although neuropeptide GPCRs are pharmacologically tractable, several obstacles limit their immediate deployment as clinical biomarkers. First, promiscuous ligand binding and near-ubiquitous tissue expression erode tumor specificity; many neuropeptide receptors, such as AT1R and NK1R, are present in normal cardiovascular, immune, and neural tissues, which complicates the interpretation of circulating receptor levels and imaging signals [47]. Second, circulating neuropeptide concentrations tend to reflect systemic neuroendocrine tone rather than intratumoral signaling, and rapid enzymatic degradation, as seen with angiotensin peptides and substance P, further curtails their value as liquid-biopsy markers [48]. Third, receptor internalization, desensitization, and alternative splicing, exemplified by the GHRH-R splice variant SV1 and the SSTR subtypes, introduce dynamic variability that static expression profiling fails to capture [49]. Fourth, standardized high-sensitivity assays are unavailable for many neuropeptide–receptor pairs, which impedes routine use in diagnostic laboratories. Finally, single-receptor readouts may lack predictive power, since neuropeptide systems operate within intricate feedback networks; decoding patient-specific network states and stratifying therapeutic responses will likely require multi-analyte signatures that integrate spatial transcriptomics, functional imaging such as ^{68}Ga-DOTATATE PET for SSTRs, and machine-learning approaches [50,51].

ACE, angiotensin-converting enzyme; Ang II, angiotensin II; DPPIV,

Table 1
Neuropeptide systems implicated in tumor progression and immune microenvironment remodeling.

Functional category	Neuropeptide / system (receptor)	Principal mechanism	Representative tumor(s)	Clinical implications / therapeutic opportunities	Ref.
Pro-proliferative / pro-angiogenic	Angiotensin II (AT1R)	Drives proliferation, angiogenesis, EMT, and stromal fibrosis	Pan-cancer	Repurposing of AT1R blockers and ACE inhibitors; AT1R as a prognostic marker	33
	GHRH (GHRH-R, SV1)	Activates the PAK1–STAT3/NF-κB inflammatory axis	Gastric cancer	GHRH-R antagonists, such as MIA-602	42
	Neuropeptide Y (Y1R/Y2R/Y5R)	Promotes hypoxia-induced proliferation and angiogenesis; DPPIV cleavage yields NPY3–36	Pediatric and gastrointestinal cancers	Y-receptor antagonists; DPPIV modulation	44
Pro-invasive / pro-metastatic	Substance P (NK1R)	Upregulates MMP-2/14; transactivates HER2/EGFR; engages AKT/mTOR and Wnt/β-catenin	Breast, colon, hepatoblastoma, GBM	Approved NK1R antagonist aprepitant (priority repurposing target)	36–38
	Neurotensin (NTSR1)	Activates Wnt/β-catenin signaling and EMT	Hepatocellular carcinoma	NTSR1-targeted agents (early stage)	45
Immunomodulatory	Substance P / HK-1 (NK1R)	HO-1-mediated M2 polarization (pro-tumor)	Pan-tumor immune microenvironment	NK1R blockade to reverse M2 skewing	39, 40
	Methionine enkephalin (OGFr)	M2-to-M1 reprogramming; MDSC suppression; PD-L1 downregulation (anti-tumor)	Colorectal cancer	Immunostimulatory adjuvant; combination with checkpoint blockade	46
Counter-regulatory / tumor-restraining	Ang-(1-7) / ACE2 (Mas)	Suppresses SOCE and PAK1/NF-κB/Snail1; restores E-cadherin; sensitizes to chemotherapy and ICB	Breast cancer	Ang-(1-7) as a chemotherapy and immunotherapy sensitizer	34, 35
Clinically established target	Somatostatin (SSTR1–5)	Antiproliferative and antiangiogenic	GEP-NETs, carcinoids, paragangliomas, meningiomas	PRRT clinically validated (most mature node)	43
	GnRH (GnRH-R)	Direct antitumor effect on GnRH-R$^+$ cells	Ovarian, breast, prostate	GnRH analogs; receptor-targeted nanoparticles	41

dipeptidyl peptidase IV; EMT, epithelial–mesenchymal transition; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; HO-1, heme oxygenase-1; MDSC, myeloid-derived suppressor cell; NTSR1 (NTR1), neurotensin receptor 1; PRRT, peptide receptor radionuclide therapy; SOCE, store-operated calcium entry; SSTR, somatostatin receptor.

3. Local neural–tumor interactions in the tumor microenvironment

3.1. Perineural invasion

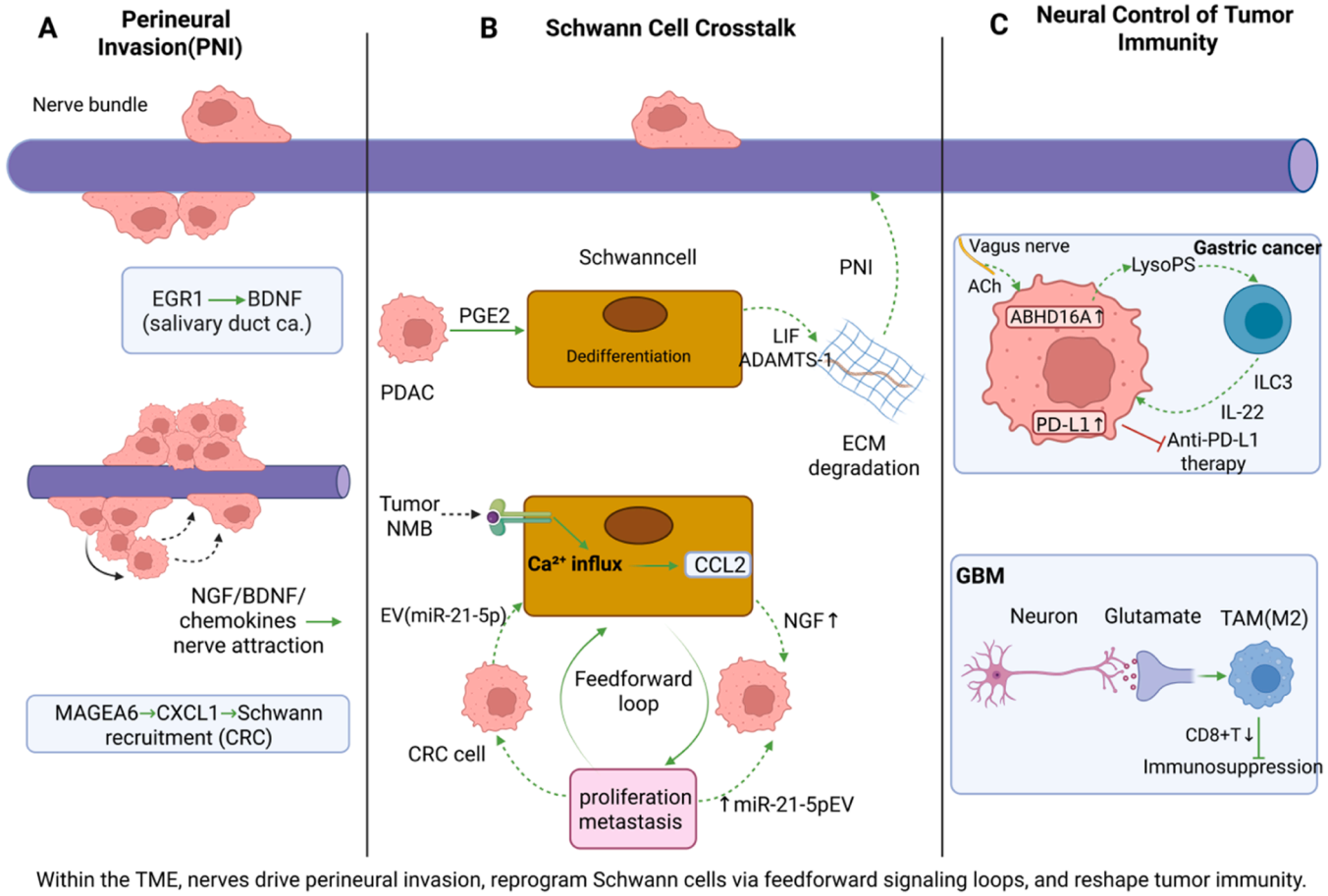
Perineural invasion (PNI) denotes a distinctive mode of tumor dissemination in which malignant cells infiltrate, encircle, and migrate along nerve bundles (Fig. 3). It is an established indicator of poor prognosis across multiple malignancies, including pancreatic, head and neck, prostate, and colorectal cancers [52,53]. Beyond providing a low-resistance conduit that facilitates locoregional recurrence and distant metastasis, PNI is frequently associated with cancer-related pain [54]. PNI is a multifactorial process involving tumor cells, neurons, glial cells, and immune cells, the mechanistic core of which resides in the dynamic interplay between tumor cells and the neural microenvironment [55,56]. Tumor cells actively promote PNI by secreting neurotrophic factors — including NGF and BDNF — and chemokines that attract nerve fibers while simultaneously inducing neural remodeling to facilitate invasion [53,57]. In salivary duct carcinoma, crosstalk between early growth response factor 1 (EGR1) and BDNF has been identified as a key driver of PNI [57]. In colorectal cancer, melanoma-associated antigen A6 (MAGEA6) stabilizes the transcription factor YY1, upregulating CXCL1 secretion to recruit Schwann cells and promote PNI [58]. Pancreatic ductal adenocarcinoma (PDAC), which exhibits an exceptionally high incidence of PNI, has become a canonical model for its study [52]. Wang and colleagues demonstrated that PDAC-derived prostaglandin E_2 (PGE_2) initiates PNI by driving Schwann cell dedifferentiation and remodeling of the neural microenvironment, thereby creating a permissive route for tumor invasion [59].

3.2. Schwann cells: mediators of neural–tumor crosstalk

Schwann cells (SCs), the principal glial cells of the peripheral nervous system, possess remarkable phenotypic plasticity that positions them as pivotal mediators of neural–tumor interactions. Co-opted by tumor cells, SCs are deeply implicated in both tumor innervation and perineural invasion [60–62]. Under physiological conditions, SCs ensheath axons to form myelin and provide trophic support; within the tumor microenvironment, however, they undergo extensive phenotypic reprogramming, transitioning from mature support cells into pro-tumorigenic effectors [63,64].

Tumor cells manipulate SC behavior through the secretion of specific signaling molecules. In PDAC, tumor-derived PGE_2 drives SC dedifferentiation, marked by upregulation of p75NTR, SOX2, and c-Jun. These dedifferentiated SCs subsequently secrete pro-invasive factors — including leukemia inhibitory factor (LIF) and ADAMTS-1 — that degrade the extracellular matrix and facilitate tumor-cell perineural invasion. Pharmacological inhibition of PGE_2 synthesis or blockade of its SC receptor substantially attenuates SC chemotaxis toward PDAC cells and neurite outgrowth, thereby suppressing PNI [59]. In cervical cancer, tumor-derived neuromedin B (NMB) activates its cognate SC receptor to trigger calcium influx, reprogramming SCs to secrete CCL2, which guides axonal regeneration and initiates PNI [65].

SCs also exert reciprocal effects on tumor cells. Colorectal cancer cells deliver miR-21-5p to SCs via extracellular vesicles, suppressing VHL expression, stabilizing HIF-1α, and upregulating NGF transcription and secretion. SC-derived NGF activates the TrkA/ERK/ELK1/ZEB1 signaling axis in cancer cells, promoting proliferation and metastasis while further augmenting miR-21-5p vesicle secretion — establishing a self-reinforcing feedforward loop [64]. SCs additionally modulate the tumor immune microenvironment through the secretion of cytokines and chemokines, fostering an immunosuppressive milieu that facilitates immune evasion [60,66]. Collectively, these findings position SCs and the signaling axes governing their tumor interactions as compelling therapeutic targets for blocking PNI and restraining tumor progression [62,63] (Fig. 3).



Within the TME, nerves drive perineural invasion, reprogram Schwann cells via feedforward signaling loops, and reshape tumor immunity.

Fig. 3. Local neural–tumor crosstalk within the tumor microenvironment: perineural invasion, Schwann-cell reprogramming, and neural shaping of tumor immunity. Green arrows denote pro-tumorigenic interactions, red arrows anti-tumorigenic interactions, and gray dashed arrows context-dependent or feedforward signaling. (A) Perineural invasion (PNI): tumor cells migrate along nerve bundles, remodeling fibers through neurotrophic factors and chemokines. EGR1–BDNF crosstalk drives PNI in salivary duct carcinoma, and MAGEA6→CXCL1 recruits Schwann cells in colorectal cancer (CRC). (B) Schwann-cell crosstalk: PDAC-derived PGE_2 drives Schwann-cell dedifferentiation and secretion of LIF and ADAMTS-1, degrading the extracellular matrix (ECM) to promote PNI; tumor-derived NMB triggers Ca^{2+} influx and CCL2 release. Reciprocally, CRC-derived extracellular vesicles deliver miR-21-5p to Schwann cells, inducing NGF that sustains a feedforward loop supporting proliferation and metastasis. (C) Neural control of tumor immunity: in gastric cancer, vagal acetylcholine engages the ABHD16A–LysoPS–ILC3–IL-22 axis to upregulate PD-L1 and blunt anti-PD-L1 therapy; in glioblastoma (GBM), glutamatergic neuron–glioma signaling polarizes tumor-associated macrophages toward an M2 phenotype and suppresses $CD8^+$ T cells, establishing local immunosuppression.

3.3. Neural regulation of the tumor immune microenvironment

The functional coupling of the nervous and immune systems is fundamental to homeostasis; within the tumor microenvironment, however, this coupling becomes a principal driver of immune evasion and malignant progression (Fig. 3). Neurotransmitters and neuropeptides released from tumor-infiltrating nerve fibers act directly on immune cells, reshaping the composition and functional state of the tumor immune microenvironment [67,68]. A well-characterized example is the immunomodulatory role of parasympathetic innervation, particularly the vagus nerve. In gastric cancer, vagally released acetylcholine upregulates expression of the lipase ABHD16A in cancer cells, promoting the biosynthesis and secretion of lysophosphatidylserine (LysoPS). LysoPS activates type 3 innate lymphoid cells (ILC3s), prompting IL-22 secretion, which subsequently induces the unfolded protein response in gastric cancer cells and upregulates programmed death-ligand 1 (PD-L1) expression — augmenting tumor immunosuppression and compromising anti-PD-L1 immunotherapy efficacy [25].

In primary brain tumors such as glioblastoma (GBM), neural–immune crosstalk is equally critical. Regions of heightened neuronal activity within GBM display pronounced local immunosuppression, characterized by enrichment of anti-inflammatory tumor-associated macrophages (TAMs) and concomitant depletion of pro-inflammatory TAMs and $CD8^+$ T cells. Mechanistically, glioma cells form glutamatergic neuron–glioma synapses that drive neuronal hyperexcitability, a state causally linked to TAM immunosuppression. Pharmacological inhibition of glutamatergic signaling shifts TAMs toward a less immunosuppressive phenotype and restores antitumor immune function [69]. Similarly, sympathetic norepinephrine modulates immune-cell function and promotes an immunosuppressive microenvironment in head and neck squamous cell carcinoma and other malignancies [24]. Collectively, these findings establish neural signaling as a principal determinant of the tumor immune landscape, and targeting neural–immune crosstalk represents a compelling strategy for enhancing antitumor immunity and circumventing immunotherapy resistance [25,67,69].

The neural–tumor interactions described above unfold within peripheral solid tumors, where nerves infiltrate from the surrounding tissue. The central nervous system, however, presents a fundamentally distinct scenario: here the tumor is embedded directly within neural tissue itself. We next examine how this unique anatomical context reshapes neural–tumor crosstalk in both primary brain tumors and brain metastases.

4. The role of the brain in primary and metastatic brain tumors

4.1. Neuron–glioma interactions in primary brain tumors

4.1.1. Synaptic communication and electrical activity in glioma

A defining feature of high-grade gliomas, including glioblastoma (GBM), is their capacity to integrate actively into the host neural circuitry — an ability that has emerged as a core mechanism underlying aggressive growth and therapeutic resistance [1,70] (Fig. 4). Glutamatergic neurons form functional chemical synapses with glioma cells, termed neuron–glioma synapses (NGS) [71,72]. Through these connections, neuronal glutamate activates AMPA receptors on the glioma-cell membrane, triggering calcium influx and membrane depolarization that directly drive tumor-cell proliferation and invasion [71, 73]. Lu et al. identified a key molecular mechanism governing NGS efficacy: free 19S proteasomes enriched at the tumor invasion front stabilize AMPA receptors at the glioma-cell surface through deubiquitinating activity, amplifying postsynaptic signal transmission and accelerating tumor progression. Pharmacological inhibition of 19S proteasome activity markedly attenuates postsynaptic potentials and suppresses tumor proliferation and invasion [71].

Electrical activity constitutes an additional axis of glioma–neuron coupling. A subpopulation of glioma cells with oligodendrocyte precursor cell (OPC)-like characteristics expresses the voltage-gated potassium channel KCND2 and elevates local extracellular potassium concentrations through potassium efflux, thereby enhancing the excitability of surrounding neurons [74]. This tumor-induced neuronal hyperexcitability not only underlies the seizures observed in many glioma patients but also reciprocally stimulates tumor growth through both synaptic and non-synaptic mechanisms, establishing a pathological feedforward cycle [75,76]. Glioma cells further exhibit neuron-like plasticity by extending tumor microtubes (TM) that interconnect individual tumor cells into networks capable of receiving synaptic input from neurons; such inputs promote de novo microtube formation and accelerate tumor-cell invasion [77]. Critically, these microtube networks confer resistance to standard-of-care therapies rather than vulnerability to them. Interconnected glioma cells redistribute cytotoxic stress through gap-junctional communication, allowing subpopulations to withstand temozolomide chemotherapy and radiotherapy by buffering this stress cooperatively [78]. TM-mediated invasion also carries tumor cells beyond surgical resection margins into regions that cytoreductive therapy cannot reach, contributing to the near-inevitable recurrence of these tumors [79]. Because current regimens, including temozolomide and radiation, fail to dismantle these intercellular structures, TM-positive tumors show shorter progression-free survival [78]. Disrupting TM formation or gap-junctional coupling therefore constitutes an unmet therapeutic need that is now under active investigation.

4.1.2. The neuroglial microenvironment: astrocytes and microglia

Under GBM influence, astrocytes undergo extensive phenotypic reprogramming, transitioning from homeostatic support cells into pro-tumorigenic effectors [80]. A central unresolved question is how a single glial population can act simultaneously as a metabolic donor and an immune suppressor. The available evidence favors integrated outputs of a shared reactive state over functionally separate subsets: GAP43-dependent mitochondrial donation [81] and ANXA1–FPR1-mediated immunosuppression [82] both depend on direct physical contact and intensify under stress, with the local microenvironment likely tipping the balance between them. They supply critical metabolic support to tumor cells: Dionysios et al. demonstrated that astrocytes transfer mitochondria directly to GBM cells via tunneling nanotubes or intercellular connections (such as GAP43-dependent

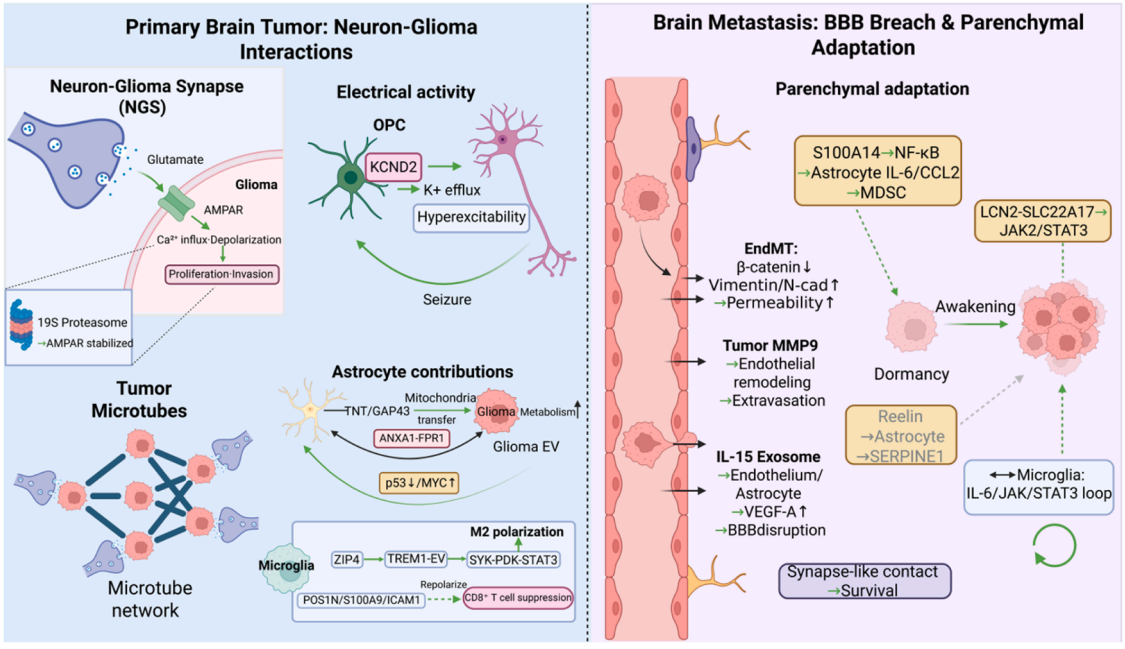


Fig. 4. Neuron–glioma interactions in primary brain tumors and tumor-cell adaptation in brain metastasis. Green arrows denote pro-tumorigenic interactions, red arrows anti-tumorigenic interactions, and gray dashed arrows context-dependent signaling. Primary brain tumor: at neuron–glioma synapses (NGS), neuronal glutamate activates AMPA receptors to trigger Ca^{2+} influx and depolarization, driving proliferation and invasion; 19S proteasomes stabilize surface AMPARs. OPC-like glioma cells expressing KCND2 raise extracellular K^+, heightening neuronal excitability and seizures, while tumor microtubes interconnect cells into an invasive network. Astrocytes support glioma metabolism through TNT/GAP43-mediated mitochondrial transfer and ANXA1–FPR1 signaling, and glioma-derived vesicles reprogram astrocytes (p53↓/MYC↑). Microglia are polarized toward an M2 phenotype via ZIP4→TREM1 vesicles and PSEN1/S100A9/ICAM1 signaling, suppressing $CD8^+$ T cells. Brain metastasis: circulating tumor cells breach the blood–brain barrier (BBB) through endothelial-to-mesenchymal transition (EndMT), MMP9-mediated endothelial remodeling, and IL-15-exosome-driven VEGF-A release. Within the parenchyma, S100A14→NF-κB and LCN2–SLC22A17→JAK2/STAT3 signaling recruits immunosuppressive myeloid cells, Reelin→SERPINE1 acts context-dependently in dormancy and awakening, and microglial IL-6/JAK/STAT3 loops together with synapse-like contacts sustain metastatic survival.

junctions), thereby augmenting tumor-cell aerobic respiratory capacity, self-renewal potential, and overall tumorigenicity [81]. Astrocytes are equally central to establishing the immunosuppressive microenvironment. Bidirectional GBM–astrocyte communication via the ANXA1–FPR1 signaling axis suppresses immunogenic tumor-cell necrosis and attenuates NF-κB and inflammasome activation in astrocytes, collectively restraining antitumor immune responses and contributing to poor prognosis [82]. Glioma-derived extracellular vesicles further induce a pro-tumorigenic astrocyte phenotype, putatively through p53 suppression and MYC pathway activation [83]. This pro-tumor consensus is directly challenged by Ribeiro et al., who reported that conditioned medium from reactive astrocytes inhibits p53-mutant GBM spheroids through GLI-1 downregulation [84].The discrepancy suggests that astrocyte polarity is gated by tumor genotype, particularly p53 status, and by whether signaling proceeds through direct contact or secreted factors. Astrocyte-directed therapy will therefore require genotype-stratified design rather than uniform astrocyte depletion.

Microglia or tumor-associated macrophages (TAMs), the brain's resident immune effectors, are typically reprogrammed toward a pro-tumorigenic M2-like phenotype in GBM, where they exert potent immunosuppressive and tumor-supporting functions. GBM cells subvert microglial identity through multiple mechanisms. Tumor cells expressing the zinc transporter ZIP4 release TREM1-containing extracellular vesicles that activate the SYK–PDK–STAT3 signaling axis in microglia, driving their polarization toward a pro-tumor state [85]. This mechanism has been validated in human glioblastoma tissue: ZIP4 expression correlates with immunosuppressive microglial gene signatures in patient tumor transcriptomes, TREM1-positive extracellular vesicles have been isolated from patient-derived glioma cell cultures and cerebrospinal fluid, and ex vivo treatment of patient-derived microglia with these vesicles recapitulates the pro-tumor polarization phenotype observed in murine models, supporting the clinical relevance of this pathway [85]. This mechanism has been validated in human glioblastoma tissue: ZIP4 expression correlates with immunosuppressive microglial gene signatures in patient tumor transcriptomes, TREM1-positive extracellular vesicles have been isolated from patient-derived glioma cell cultures and cerebrospinal fluid, and ex vivo treatment of patient-derived microglia with these vesicles recapitulates the pro-tumor polarization phenotype observed in murine models, supporting the clinical relevance of this pathway [85]. Tumor-secreted factors — including POSTN [86], S100A9 [87], and ICAM1 [88] — recruit and repolarize microglia via the αVβ3/PI3K/AKT/NF-κB, αVβ3-integrin/AKT1/TGF-β1, and FASN–-STAT1–ICAM1 pathways, respectively, culminating in $CD8^+$ T cell suppression and consolidation of an immunosuppressive niche. Although multiple axes, including ZIP4–TREM1, POSTN, S100A9, and ICAM1, converge on M2-like polarization, only ZIP4–TREM1 has been validated in human tissue [85], which marks it as the most credible near-term target. This crosstalk is a principal determinant of GBM malignancy, yet its therapeutic exploitation hinges on identifying nodes that are at once non-redundant and druggable.

4.2. Brain metastasis: tumor-cell breach of and adaptation to the central nervous system

Brain metastasis is a multistep cascade in which extravasation across the blood–brain barrier (BBB) constitutes the decisive rate-limiting step [89]. The BBB comprises brain microvascular endothelial cells interconnected by tight junctions, reinforced by pericytes and astrocytic end-feet, which together impose a stringent physical and biochemical barrier on molecular and cellular transit into the central nervous system [90]. To successfully colonize the brain, circulating tumor cells must develop unique strategies to breach this formidable barrier. Brain-tropic tumor cells (such as triple-negative breast cancer cells) can actively induce endothelial-to-mesenchymal transition (EndMT) in brain microvascular endothelial cells. During this process, the expression of endothelial markers such as β-catenin is downregulated, while mesenchymal markers such as vimentin and N-cadherin are upregulated, leading to loosened cell junctions and increased permeability that facilitate transendothelial migration of tumor cells [91].

Beyond phenotypic reprogramming of endothelial cells, tumor cells can directly compromise BBB structural integrity. Following arrest in brain microvessels, metastatic cells from tumors such as lung cancer secrete matrix metalloproteinase 9 (MMP9), which induces neighboring endothelial cells to undergo active morphological remodeling and protrusion formation, ultimately facilitating cancer-cell extravasation. Pharmacological inhibition of MMP9 markedly reduces endothelial remodeling and extravasation, establishing direct cancer cell–endothelial cell crosstalk as a critical determinant of this process [89]. During BBB transit, breast cancer cells can additionally induce localized vasoconstriction and form intraluminal endothelial plugs — putatively to shield invading cells from hemodynamic forces — before traversing the barrier transcellularly and inducing vascular abnormalities including multilumen vessels and endothelial blebbing. The partial resolution of these alterations after tumor-cell transmigration illustrates the dynamic and reversible responsiveness of the BBB to metastatic invasion [92]. Tumor-derived cytokines and exosomes can also compromise BBB integrity at a distance: cytokines and IL-15-containing exosomes released by leukemia cells are internalized by brain endothelial cells and astrocytes, inducing VEGF-A production that disrupts barrier function [93].

After successfully crossing the BBB, disseminated tumor cells must survive, adapt, and ultimately proliferate in the unique "foreign soil" of the brain parenchyma to form metastases. This process depends heavily on complex bidirectional interactions and mutual remodeling between tumor cells and brain-resident cells [94,95]. Tumor cells that enter the brain parenchyma frequently exist in a reversible dormant state. The brain microenvironment regulates the dormancy and reawakening of these dormant tumor cells through multicellular crosstalk and biomechanical cues from the extracellular matrix, which is a key cause of brain-metastasis recurrence [96]. Astrocytes and microglia are the two central resident populations shaping the brain-metastatic microenvironment. Lung and breast cancer cells engage the S100A14–TLR4–NF-κB axis to stimulate astrocytic secretion of IL-6 and CCL2, recruiting myeloid-derived suppressor cells (MDSCs) and establishing local immunosuppression [97]; the LCN2–SLC22A17–JAK2/-STAT3 pathway similarly activates astrocytes and promotes macrophage recruitment [98]. Small-cell lung cancer recruits reactive astrocytes through Reelin secretion; these astrocytes in turn sustain tumor growth by providing neurotrophic factors including SERPINE1, recapitulating neuron–glia interactions characteristic of brain development [99]. Concurrently, melanoma brain-metastasis cells and microglia engage in a self-reinforcing IL-6/JAK/STAT3 signaling loop that enhances tumor viability and metastatic capacity [99]. Certain tumors additionally integrate into host neural circuits by forming synapse-like contacts, exploiting this electrophysiological coupling to sustain parenchymal survival [100] (Fig. 4).

Across systemic, local, and central scales alike, the nervous system emerges as an active driver of tumor progression. This relationship is nonetheless reciprocal: just as the nervous system shapes tumors, tumors profoundly perturb nervous-system homeostasis, and both dimensions ultimately converge on clinical practice. We therefore turn next to the remote neurological consequences of cancer and to the therapeutic opportunities that arise from targeting the brain–tumor axis.

5. Clinical manifestations and therapeutic implications of the brain–tumor axis

5.1. Remote effects of tumors on the nervous system: pain, cognitive impairment, and cachexia

The bidirectional nature of the brain–tumor axis is manifest not only in neural regulation of tumor biology but also in the broad remote effects

that tumors and their treatments exert on the nervous system, principally as cancer-related pain, cognitive impairment, and cachexia. Cancer-induced bone pain (CIBP) ranks among the most refractory pain syndromes, involving sensitization of both peripheral and central nervous systems [101,102]. Peripherally, inflammatory mediators and growth factors released by tumor cells and their microenvironment directly activate and sensitize nociceptors [101]. Centrally, ascending nociceptive signals reach the dorsal horn of the spinal cord, where they trigger microglial and astrocytic activation [103,104]. Activated glia release pro-inflammatory cytokines — including IL-18 — and chemokines that amplify synaptic transmission through neuro-immune and glia–neuron crosstalk, producing central sensitization and rendering CIBP particularly refractory to treatment [105–107]. Additionally, substance P and the chemokines CCL2 and CCL3 mediate stage-specific macrophage recruitment to the dorsal root ganglia, establishing a neuro-immune feedforward loop that exacerbates pain [106].

Cancer-related cognitive impairment (CRCI), commonly termed chemotherapy-associated cognitive dysfunction, constitutes a major determinant of quality of life in cancer survivors [108]. Although its mechanisms remain incompletely elucidated, converging evidence implicates systemic inflammation, neuroendocrine dysregulation, and direct or indirect neural circuit injury attributable to both the tumor and its treatment [109,110]. Buskbjerg and colleagues conducted a study enrolling 40 testicular cancer patients following orchiectomy and 22 healthy controls, combining neuropsychological assessment with magnetic resonance imaging, and reported a higher incidence of post-orchiectomy cognitive impairment in patients — an effect potentially mediated by alterations in endocrine status, including androgen levels, and by androgen receptor gene polymorphisms [109].

Cachexia is a complex metabolic syndrome defined by progressive weight loss and involuntary wasting of skeletal muscle and adipose tissue. A central pathogenic driver is tumor-induced neuroinflammation, particularly within the hypothalamus [111]. Inflammatory factors produced by tumor cells (such as PGE_2) can cross the BBB and, either directly or by amplifying the effects of gut-derived pathogen-associated molecular patterns, activate inflammatory pathways such as NF-κB in the hypothalamus, leading to anorexia and increased energy expenditure [112]. Tumor-derived signals additionally engage the sympathetic nervous system to promote the thermogenic reprogramming of white adipose tissue into beige adipocytes — a process termed adipose browning — further exacerbating energy wasting and weight loss [113].

5.2. *Emerging therapeutic strategies targeting neural–tumor interactions*

Advancing mechanistic understanding of the brain–tumor axis has positioned neural–tumor interactions as a compelling therapeutic frontier [3,4,8,114]. Emerging strategies aim to suppress tumor growth, metastasis, and therapeutic resistance by intervening in central–peripheral neural connectivity, blocking local neurotransmitter signaling, or modulating neuro-immune crosstalk (Fig. 5).

Approaches targeting the sympathetic nervous system have attracted particular interest. β-adrenergic receptor antagonists (β-blockers), widely prescribed antihypertensive agents, suppress sympathetically driven tumor-cell proliferation and angiogenesis in preclinical models across multiple cancer types [24,115]. In renal cell carcinoma, combining β-blockers with PD-1 inhibitors shows promise for reversing T cell exhaustion and augmenting immunotherapy efficacy [67]. Selective surgical denervation has similarly demonstrated the capacity to inhibit tumor growth in certain experimental models [115].

Interventions targeting central regulatory circuits represent an equally promising avenue. Given that cancer-induced anxiety promotes breast cancer progression through CRH neuron activation in the central medial amygdala (CeM), the anxiolytic alprazolam has been shown to attenuate tumor growth in murine models, raising the possibility that mood-stabilizing agents may harbor intrinsic antitumor activity [12].

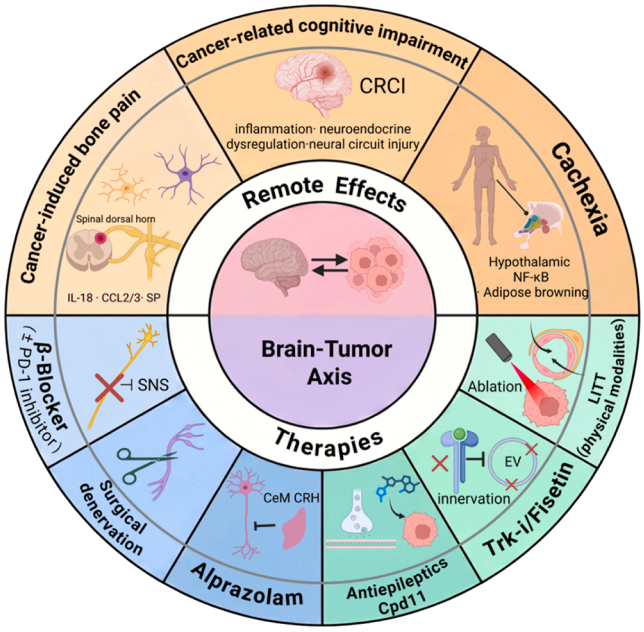


Fig. 5. Emerging therapeutic strategies targeting the brain–tumor axis. Mechanistic insights into neural–tumor interactions have yielded interventions operating at three levels. Systemic and sympathetic modulation: β-adrenergic receptor antagonists (β-blockers) suppress sympathetically driven proliferation and angiogenesis and, combined with PD-1 inhibitors, reverse T-cell exhaustion in renal cell carcinoma, while selective surgical denervation restrains tumor growth in experimental models. Central-circuit intervention: because amygdalar CRH-neuron activation promotes tumor progression, the anxiolytic alprazolam attenuates tumor growth, pointing to intrinsic antitumor activity of mood-stabilizing agents. Local neuron–tumor and neuro-immune targeting: antiepileptic agents and a blood–brain-barrier-penetrant celecoxib derivative (compound 11) curb neuronal-activity-driven proliferation and PGE2-induced hyperexcitability and chemoresistance in glioblastoma; Trk-receptor inhibition blocks tumor-induced neurogenesis and perineural invasion; and the flavonoid fisetin prevents neuronal internalization of m6A-modified tumor extracellular vesicles in pancreatic cancer. Physical modalities such as laser interstitial thermal therapy (LITT) ablate tumor, transiently disrupt the blood–brain barrier to enhance drug delivery, and release damage-associated molecular patterns that promote antitumor immunity.

At the local tumor level, disrupting direct neuron–tumor cell communication constitutes an additional strategic axis. In GBM, where neuronal activity drives tumor proliferation, specific antiepileptic agents have been found to potentially retard tumor progression [75]. Shen and colleagues developed a blood–brain barrier-penetrant celecoxib derivative (compound 11) that effectively suppresses PGE_2-induced neuronal hyperexcitability and overcomes chemoresistance in GBM [116]. Targeting neurotrophic factor signaling — including Trk receptor inhibition — to block tumor-induced neurogenesis and perineural invasion has shown promise in both preclinical models and early-phase clinical trials [115]. In pancreatic cancer, the natural flavonoid fisetin prevents neuronal internalization of tumor-derived extracellular vesicles carrying aberrantly m^6A-modified transcripts, thereby suppressing stress-driven pathological innervation and tumor progression [17].

Although neural-targeted therapies hold considerable promise, disrupting homeostatic pathways raises important safety considerations. Chronic β-adrenergic blockade may precipitate fatigue, depression, sleep disturbance, and cognitive slowing, symptoms that overlap with cancer-related sequelae and thereby complicate clinical attribution [20]. Pan-Trk inhibitors such as larotrectinib and entrectinib can induce peripheral neuropathy, dizziness, ataxia, and cognitive impairment, reflecting the disruption of neuronal maintenance and synaptic plasticity [117]. Physical neuromodulation, including vagal nerve

stimulation and surgical sympathectomy, carries the risk of autonomic dysregulation such as orthostatic hypotension and gastrointestinal dysmotility [118]. Interventions aimed at central circuits, including anxiolytics and antiepileptics, may cause sedation, motor incoordination, and mood alteration [119]. The therapeutic window remains poorly defined, and doses sufficient to restrain tumor growth may approach the threshold for neurological compromise. Future trials will need to incorporate neurocognitive monitoring, patient-reported outcomes, and adaptive dosing [120], while tumor-selective delivery platforms, including nanoparticles and conditionally activated prodrugs, may limit systemic exposure without sacrificing intratumoral efficacy [121].

Three structural barriers further constrain clinical translation. First, many high-value targets reside within the CNS, yet most candidate agents lack adequate blood–brain barrier penetrance, leaving purpose-built CNS-penetrant derivatives such as compound 11 [116] the exception rather than the rule. Second, because the targeted pathways are physiological rather than tumor-specific, on-target off-tumor neurotoxicity is an intrinsic liability; inhibition of neurotrophic (NGF/TrkA) or neurotransmitter signaling that sustains neuronal maintenance and autonomic function produces effects mechanistically inseparable from the intended antitumor action, which narrows the therapeutic window [117]. Third, trial design poses distinctive difficulties. Neuromodulatory effects are slow and mediated through immune and stromal compartments, which renders conventional tumor-shrinkage endpoints insensitive; pharmacodynamic biomarkers of neural engagement remain undefined; and distinguishing direct antitumor effects from indirect benefits conferred by improved mood or reduced stress, as with β-blockers or anxiolytics, demands controlled designs seldom applied in oncology [19,20]. Overcoming these obstacles will require the parallel development of CNS-penetrant chemistry, tumor-restricted delivery, validated neural-engagement biomarkers, and adaptive trial frameworks.

Despite these safety considerations and structural barriers, physical modalities for remodeling the neural tumor microenvironment hold considerable therapeutic potential when implemented with appropriate risk mitigation. Laser interstitial thermal therapy (LITT) not only achieves direct tumor ablation but transiently disrupts the BBB to enhance delivery of chemotherapeutic and immunotherapeutic agents, and may potentiate antitumor immunity through the release of damage-associated molecular patterns, facilitating the conversion of immunologically quiescent tumors to inflamed phenotypes [122]. Collectively, these strategies delineate a therapeutic framework grounded in nervous system modulation and herald a conceptual transition from tumor-centric to brain–tumor-axis-based treatment paradigms [1,70].

6. Conclusions

The emerging concept of the "brain–tumor axis" is fundamentally reframing our understanding of cancer biology. We propose that neural–tumor crosstalk warrants recognition as an emerging integrative hallmark of cancer, one that modulates established hallmarks such as immune evasion, angiogenesis, and metabolic reprogramming through neuro-immune and neuro-vascular interfaces. Its unifying feature is the context-dependent duality of neural signaling. Parasympathetic innervation expands the cancer stem-cell pool in gastric cancer yet restrains early pancreatic cancer, and glutamatergic transmission drives glioma proliferation whereas its pharmacological modulation proves antitumor. Identifying the molecular rheostats that govern these transitions is the central challenge of cancer neuroscience. Accumulating evidence demonstrates that the brain and its extended nervous system are not passive bystanders during tumor progression, but active regulators of tumor initiation, metastasis, and therapeutic resistance [1,2]. This regulatory influence operates across multiple scales: systemic modulation of distant tumors via stress-response pathways and central–peripheral neural circuits; local crosstalk among neurons, glial cells, and malignant cells within the tumor microenvironment; functional integration of primary brain tumors into existing neural circuits; and the breach and subsequent adaptation of metastatic cancer cells to the barriers of the central nervous system [3,4,6]. Together, these bidirectional interactions constitute a finely orchestrated regulatory network whose full complexity is only beginning to be appreciated.

Targeting neural–tumor interactions has consequently emerged as a promising therapeutic avenue. Strategies under investigation include the repurposing of existing agents—such as β-adrenergic blockers and anxiolytics [12,115]—the development of selective inhibitors of neural signaling pathways (e.g., Trk, PGE2) [59,116], and the application of physical interventions such as laser interstitial thermal therapy (LITT) to remodel the neural microenvironment [122]. Looking ahead, several priorities warrant particular attention: deploying high-resolution tools such as spatial transcriptomics to construct increasingly granular maps of neural–tumor–immune interaction landscapes [67]; engineering drug-delivery platforms capable of selectively targeting defined neural circuits or signaling mediators; and establishing optimal combinatorial regimens that integrate neuromodulatory approaches with standard chemotherapy, radiotherapy, and immunotherapy [3,8]. The paradigm shift from a tumor-centric perspective to one grounded in the brain–tumor axis [70] signals the growing centrality of cancer neuroscience within the broader framework of precision oncology.

Ethics approval

Not applicable.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

Yuxin Liu: Writing – original draft, Conceptualization. **Chunyuan Guo:** Formal analysis, Data curation, Conceptualization. **Xing Wang:** Methodology, Investigation. **Kaimeng Huang:** Visualization, Supervision. **Shan Huang:** Software, Project administration, Methodology. **Jing Cao:** Supervision, Software, Resources. **Minchao Deng:** Resources, Project administration, Methodology. **Tao Guan:** Software, Resources, Project administration. **Yu Zhang:** Visualization, Validation, Supervision. **Shaodan Tian:** Resources, Methodology, Investigation. **Zhi Zheng:** Writing – review & editing, Validation, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and material

No new data was created or analyzed in this study. Data sharing is not applicable to this article.

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