Trends in Cancer

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Review

Neuron–tumor communication in solid tumors: from bona fide synapses to pseudo-synaptic neural interfaces☆

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Neuron–tumor communication is emerging as a distinct layer of tumor–host interaction beyond conventional stromal, vascular, and immune regulation. Recent studies show that malignant cells can detect neuronal activity and convert neural signals into growth-promoting cellular responses. In the brain, glioma cells can become electrically integrated into neuronal circuits, where glutamatergic input drives depolarization, calcium influx, and downstream signaling. In extracranial tumors, neural influence appears more heterogeneous, involving spatially organized neurochemical niches, receptor-enriched cancer–nerve contacts ('pseudo-synapses'), autonomic pathways, and injury-associated neuroimmune remodeling. These findings raise important questions about how neural input regulates tumor cell state, metabolism, immune tone, and therapeutic adaptation. This review evaluates the evidence linking neural activity to cancer progression across anatomical contexts and outlines the experimental standards needed to distinguish structured neuron–tumor interfaces from broader neural effects within the tumor microenvironment.

Highlights

Neuron–tumor communication exists along a spectrum, ranging from bona fide synapses to pseudo-synaptic interfaces.

Pseudo-synapses may fulfill canonical synaptic ultrastructure while exhibiting noncanonical signaling outputs.

Peripheral tumors may exploit localized neurotransmitter signaling without fully mature synaptic architecture.

Defining neural dependencies may enable neuro-targeted cancer therapies.

Neuron–tumor communication as an emerging dimension of the tumor ecosystem

The contemporary tumor ecosystem framework increasingly recognizes nonmalignant host-derived components as active regulators of tumor progression [1]. Alongside immune cells [2], fibroblasts [3,4], and the vasculature [5], the nervous system has emerged as an additional functional component capable of shaping tumor behavior across multiple cancer types [6–8]. Emerging studies suggest that cancer cells can engage neurons through multiple modes of communication, including bona fide synapses, pseudo-synaptic interfaces, and broader neuropeptide- or circuit-dependent regulation [9–21]. However, despite the rapid expansion of this field, the structural and functional criteria distinguishing these interaction states remain incompletely defined.

A central unresolved issue is whether these diverse interactions represent fundamentally distinct biological entities or a functional continuum of neuron–tumor communication. This conceptual question is particularly important in peripheral solid tumors, where functional coupling between neuronal activity and tumor-cell signaling is increasingly recognized. Yet, the functional properties of neuron–tumor interfaces remain incompletely characterized, despite accumulating ultrastructural evidence that some peripheral neuron–tumor contacts can exhibit the architectural hallmarks of bona fide synapses. Functional neurotransmitter responsiveness alone may, therefore, not necessarily constitute proof of classical synaptic

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architecture, underscoring the need to distinguish localized neurotransmitter signaling from rigorously validated synaptic organization.

Accordingly, the central aim of this review is not to comprehensively catalog tumor innervation but to define how distinct morphological and functional states of neuron–tumor communication can be classified and interpreted across intracranial and extracranial cancers. We focus particularly on the continuum from bona fide synapses to pseudo-synaptic interfaces and discuss the unresolved structural, electrophysiological, and functional criteria required to distinguish these states across different tumor contexts. Representative studies across tumor types are summarized in Table 1.

Direct neuron–tumor communication from bona fide synapses to pseudo-synaptic interfaces

Based on the recognition of neuron–tumor communication as an emerging component of the tumor ecosystem, recent studies indicate that neurons can influence cancer cells through direct and spatially organized forms of communication, ranging from bona fide synapses to synapselike or pseudo-synaptic interfaces.

We use the term bona fide synapse to denote a neuron–tumor junction that satisfies both canonical ultrastructural and functional criteria of chemical synapses, including presynaptic active-zone

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Table 1. Representative studies of neuron–tumor synaptic and circuit interactions across tumor types

Tumor type	Neural component	Mode of interaction	Major mediator(s)	Principal conclusion	Refs	Year
HGG	Cortical excitatory neurons	Activity-dependent paracrine signaling	NLGN3	Neuronal activity promotes HGG growth through secretion of NLGN3	[9]	2015
Glioma	Neurons	Bona fide neuron–glioma synapses	AMPAR-mediated glutamatergic input	Functional neuron-glioma synapses drive glioma growth and invasiveness	[10]	2019
HGG	Neurons	Electrical and synaptic integration into neural circuits	AMPAR-mediated glutamatergic input	Synaptic and electrical neuron–glioma integration drives HGG progression	[11]	2019
B2BM	Glutamatergic neurons	Pseudo-tripartite synapse	Glutamate; GRIN2B–NMDAR	Neuronal glutamatergic signaling supports B2BM brain colonization	[12]	2019
Glioma	Neurons	BDNF-regulated malignant synaptic plasticity	BDNF–TrkB; AMPA receptors	BDNF–TrkB signaling enhances malignant synaptic plasticity	[13]	2023
GBM	Callosal projection neurons	Activity-dependent neuron–tumor communication	SEMA4F	Remote neuronal activity promotes GBM progression and infiltration via SEMA4F	[14]	2023
DMG	GABAergic neurons	Functional neuron–cancer synapses	$GABA_AR$; NKCC1	GABAergic synapses drive DMG proliferation via $GABA_AR$ and NKCC1	[15]	2025
GBM	Local and long-range neurons	Integration into local and long-range neural circuits	Acetylcholine; CHRM3	Cholinergic input promotes GBM motility through CHRM3	[16]	2025
GBM	Cancer-connected neurons	Retrograde-traced neuron–tumor networks	Cholinergic signaling	Cholinergic neurons drive GBM invasion	[17]	2025
SCLC	Vagal sensory or cortical neurons	Functional neuron–tumor synapses	NMDAR; $GABA_AR$	Synaptic inputs from neurons promote SCLC proliferation	[18]	2025
PDAC	Sensory neurons	Glutamatergic pseudo-synapse	Glutamate; GRIN2D–NMDAR	Sensory neuron-cancer pseudo-synapses promote PDAC progression	[19]	2025
GC	$CGRP^+$ peptidergic sensory neurons	Direct peptidergic neuron–tumor interaction	NGF; CGRP; calcium signaling	Sensory neuron connectivity promotes GC growth and metastasis	[20]	2025
SCLC	Vagal and cortical neurons	Paracrine and neuron–tumor interactions	Glutamatergic and GABAergic signaling	Neuronal activity drives SCLC growth in the lung and brain	[21]	2025

DMG: diffuse midline glioma; GABA: γ-aminobutyric acid; $GABA_AR$: $GABA_A$ receptor; GBM: glioblastoma; PDAC: pancreatic ductal adenocarcinoma; GC, gastric cancer; HGG, high-grade glioma; GRIN2B: glutamate ionotropic receptor NMDA type subunit 2B; GRIN2D: glutamate ionotropic receptor NMDA type subunit 2D; BDNF: brain-derived neurotrophic factor; TrkB: tropomyosin receptor kinase B; SEMA4F: semaphorin 4F; NKCC1: Na^+-K^+-$2Cl^-$ cotransporter 1; CHRM3: cholinergic receptor muscarinic 3.

organization with docked vesicles, a defined synaptic cleft, postsynaptic density formation with appropriate scaffolding proteins and receptor complexes, and activity-dependent electrophysiological coupling. By contrast, pseudo-synaptic interfaces refer to spatially restricted neuron–tumor signaling assemblies that can exhibit the full ultrastructural repertoire of classical chemical synapses, including presynaptic vesicles, synaptic clefts, postsynaptic densities, and synaptic scaffold proteins [19], yet currently lack evidence that signal transmission across these interfaces recapitulates the defining physiological properties of canonical synapses, including quantal transmission, classical excitatory/inhibitory postsynaptic potentials (EPSPs/IPSPs), characteristic synaptic kinetics, or activity-dependent plasticity (See Table 2).

This distinction is functionally important because bona fide synapses imply rapid, spatially precise transmission characterized by canonical electrophysiological outputs, whereas pseudo-synaptic interfaces may generate noncanonical downstream responses, including large intracellular calcium transients and calcium waves, without currently demonstrated EPSP-like responses, quantal transmission, or classical synaptic plasticity.

Table 2. Proposed criteria distinguishing bona fide neuron–tumor synapses from pseudo-synaptic neuron–tumor interfaces

Feature	Bona fide neuron–tumor synapse	Pseudo-synaptic neuron–tumor interface
Definition	Neuron–tumor junction fulfilling canonical structural and physiological criteria of a chemical synapse	Neuron–tumor junction that may fulfill canonical structural criteria but whose physiological properties remain incompletely defined
Presynaptic vesicles	Present	Present
Presynaptic active zone organization	Present	Present or incompletely characterized
Synaptic cleft	Present	Present
PSD	Present	Present
Neurotransmitter receptor enrichment	Present	Present
Activity-dependent neurotransmitter release	Present	Present
Electrophysiological coupling	Demonstrated	Not yet established
Quantal transmission	Demonstrated	Unknown
Classical EPSP/IPSP generation	Demonstrated	Unknown
Action-potential-coupled responses	Demonstrated	Unknown
Synaptic kinetics (millisecond-scale transmission)	Demonstrated	Unknown
Activity-dependent synaptic plasticity	Demonstrated	Unknown
Dominant downstream response	Membrane depolarization and canonical postsynaptic electrical signaling	Calcium influx and calcium-wave propagation
Representative tumor types	Glioma, diffuse midline glioma, SCLC	PDAC, B2BM pseudo-tripartite niches
Current major unresolved question	Functional contribution to tumor evolution	Whether signaling exhibits the defining physiological hallmarks of canonical synaptic transmission

Bona fide synapses

Among the diverse modes of neuron–tumor interaction, bona fide synapses provide strong evidence that neuronal activity can directly regulate cancer cells (Figure 1A). In the strict neurobiological sense, bona fide synapses are typically characterized by presynaptic active zones containing docked synaptic vesicles, synaptic clefts of defined nanoscale dimensions, postsynaptic densities enriched with scaffolding proteins such as postsynaptic density protein 95 (PSD-95), postsynaptic membranes bearing appropriate receptor complexes, and activity-dependent electrophysiological coupling. Importantly, the postsynaptic density is not merely a structural feature but a molecular signaling platform that clusters receptors, links them to second-messenger cascades, and regulates synaptic strength through receptor density and subunit composition.

Through these synapse-like structures, neurons transmit electrochemical signals to tumor cells through structures resembling conventional neuron–neuron synapses, enabling neuronal firing to be converted into intracellular signaling events in malignant cells [11,16]. This mechanism was first established in gliomas, where neurons form glutamatergic synapses onto tumor cells, and neuron-derived glutamate activates postsynaptic α-amino-3-hydroxy-5-methyl-4-

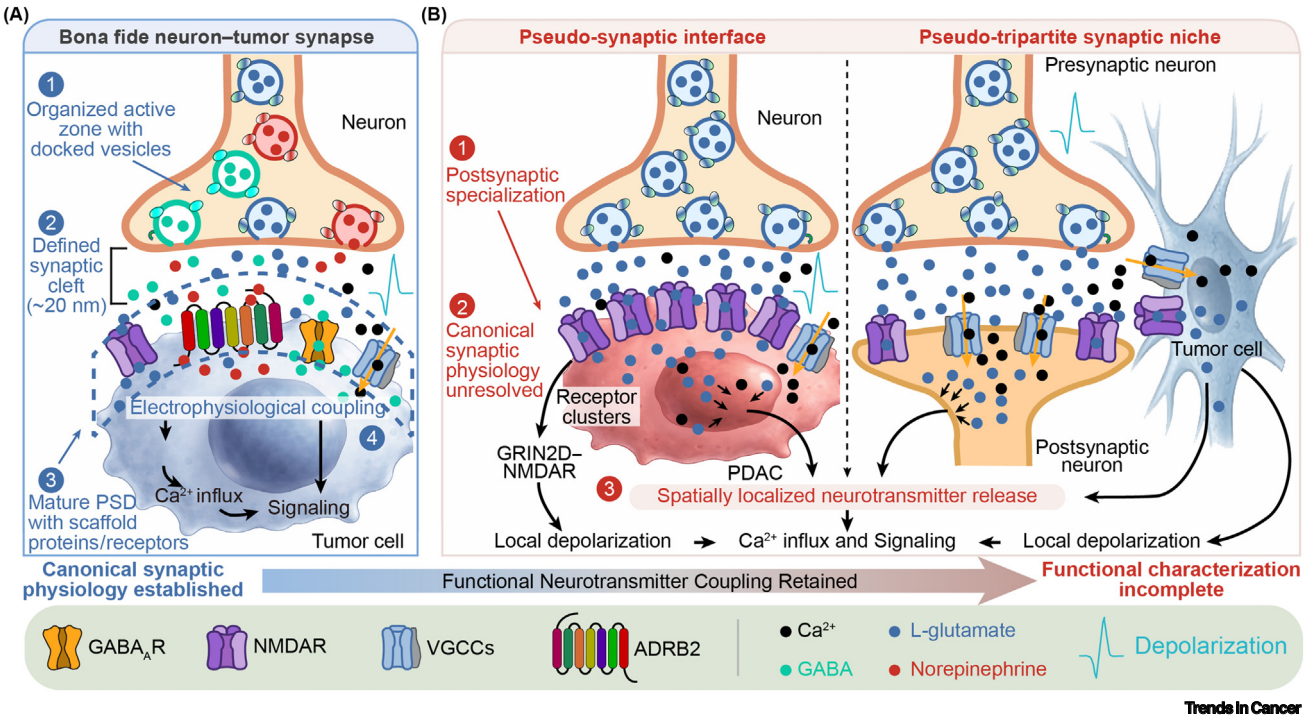

Figure 1. Direct neuron–tumor communication across a synaptic continuum. (A) Bona fide neuron–tumor synapses exhibit coordinated ultrastructural and functional features of classical chemical synapses, including organized presynaptic active zones with docked vesicles, defined synaptic clefts, mature postsynaptic density (PSD) scaffolds, receptor enrichment, and activity-dependent electrophysiological coupling. Neurotransmitter release induces membrane depolarization, Ca^{2+} influx, and downstream signaling in tumor cells. (B) Synapselike and pseudo-synaptic interfaces retain localized neurotransmitter-responsive signaling despite progressively reduced structural organization. In PDAC, sensory neuron–tumor contacts exhibit presynaptic vesicles, synaptic clefts, postsynaptic densities, synaptic scaffold proteins, receptor clustering, and GRIN2D-containing N-methyl-D-aspartate receptor (NMDAR)-dependent glutamate sensing, thereby fulfilling the currently recognized ultrastructural hallmarks of chemical synapses. However, these interfaces predominantly induce calcium influx and calcium-wave signaling, while whether they exhibit quantal transmission, classical EPSP-like responses, or synaptic plasticity remains unknown. In pseudo-tripartite synaptic niches, tumor cells exploit neurotransmitter release from adjacent neuronal synapses without forming direct canonical synaptic junctions. Across this continuum, structural specialization progressively decreases while localized neurotransmitter coupling and downstream signaling are retained. ADRB2: β_2 adrenoreceptor; GABA: γ-aminobutyric acid; $GABA_AR$: $GABA_A$ receptor; VGCCs: voltage-gated calcium channels; PDAC: pancreatic ductal adenocarcinoma; GRIN2D: glutamate ionotropic receptor NMDA type subunit 2D; EPSP: excitatory postsynaptic potential. Parts of the figure created using BioRender (https://BioRender.com).

isoxazolepropionic acid receptor (AMPAR) on malignant cells, leading to membrane depolarization, Ca^{2+} influx, and downstream signaling pathways that support malignant growth [11]. These studies established that malignant cells can act as bona fide postsynaptic partners and provided a direct mechanistic link between neuronal firing and tumor-cell signaling. Earlier work further identified neuronal activity-regulated secretion of neuroligin-3 (NLGN3) as a mitogenic mechanism in high-grade glioma, activating phosphoinositide 3-kinase–mechanistic target of rapamycin (PI3K–mTOR) signaling and feedforward NLGN3 expression in tumor cells [9].

In diffuse midline gliomas, γ-aminobutyric acid (GABA)-ergic interneurons form functional synapses with malignant cells through γ-aminobutyric acid type A ($GABA_A$) receptors. Because these tumor cells maintain elevated intracellular chloride levels, GABA signaling is depolarizing rather than inhibitory [15]. These findings indicate that the biological consequences of synaptic input depend not only on the presynaptic neuron but also on the electrophysiological state of the tumor cell, highlighting that neuron–tumor synapses are defined not solely by neurotransmitter identity but also by the electrophysiological state of the malignant cell receiving the input. Consistent with this, epigenomic and chromatin-interactome analyses in glioblastoma have identified gene programs associated with synapse organization and axon guidance [22].

Bona fide synaptic communication is not restricted to primary brain tumors. In small cell lung cancer (SCLC), tumor cells also form functional synapses with neurons and receive glutamatergic and GABAergic inputs, which induce postsynaptic currents and Ca^{2+} transients [18,21]. Taken together, these studies indicate that direct synaptic neuron–tumor communication is not confined to the central nervous system and may represent a broader mechanism by which neuronal activity is coupled to malignant growth.

Whether neuron–tumor interfaces in peripheral cancers satisfy the full physiological criteria of canonical synaptic transmission remains unresolved, even when ultrastructural criteria appear to be fulfilled. Nerve–cancer contacts in extracranial tissues are likely rare, small, and obscured by complex stroma containing glial, immune, and epithelial elements. Systematic electron microscopy in human pancreatic cancer has shown that these interfaces contain defining ultrastructural hallmarks of bona fide synapses, including synaptic clefts of defined width, vesicle docking, active-zone-like presynaptic specializations, and organized postsynaptic densities [19]. However, it remains unclear whether these pseudo-synapses exhibit the quantal transmission properties, electrophysiological kinetics, and plasticity that define canonical neuronal synapses. Functional neurotransmitter responsiveness alone should not automatically be interpreted as proof of classical synaptic organization.

Synapselike and pseudo-synaptic interfaces

In addition to bona fide synapses, cancer cells can engage neurons through synapselike or pseudo-synaptic interfaces that may satisfy the ultrastructural criteria of classical synapses yet currently exhibit distinct or incompletely characterized physiological outputs compared with canonical neuronal synapses (Figure 1B) [19,23]. PDAC provides a prototypical example of this mode of interaction [19]. Sensory neurons form direct contacts with PDAC cells that display presynaptic vesicles, a defined synaptic cleft, postsynaptic densities, and postsynaptic scaffold proteins, collectively recapitulating the ultrastructural hallmarks of classical chemical synapses. At these interfaces, tumor cells selectively express the N-methyl-D-aspartate receptor (NMDAR) subunits, including glutamate ionotropic receptor NMDA type subunit 2D (GRIN2D) and the associated glutamate ionotropic receptor NMDA type subunit 1 (GRIN1), enabling them to respond to neuron-derived glutamate. Disruption of this glutamate–GRIN2D axis suppresses tumor progression in vivo, supporting a functional role for these contacts. Glutamate release at these interfaces

induces prominent calcium influx and calcium-wave propagation in tumor cells. However, whether these responses represent quantal synaptic transmission, generate classical EPSP-like events, or exhibit activity-dependent synaptic plasticity remains unknown. Localized neurotransmitter-responsive signaling at these interfaces may engage downstream effectors such as voltage-gated calcium channels. Nonetheless, it is now established that cancer-cell depolarization and calcium influx can be linked to a tumor-cell-specific postsynaptic receptor configuration, suggesting that at least some peripheral cancers establish highly selective receptor-enriched neural interfaces rather than merely responding to diffusible neurotransmitter pools.

A conceptually related but anatomically distinct configuration has been described in breast-to-brain metastases (B2BM) [12]. In this context, metastatic tumor cells exploit a pseudo-tripartite synaptic microenvironment in which glutamate released from neighboring neuronal synapses activates NMDAR-dependent signaling in tumor cells. Rather than forming fully mature synaptic structures, tumor cells utilize pre-existing synaptic niches to access localized neurotransmitter signals. Additional studies suggest that such neural niche interactions may occur early during metastatic progression [24–26]. These findings further support the concept that tumor cells exploit localized neurotransmitter signaling without necessarily forming fully canonical synaptic structures.

Collectively, these observations suggest that direct neuron–tumor communication is better conceptualized as a functional continuum rather than a binary distinction between 'synaptic' and 'nonsynaptic' signaling [12,19,23,27,28]. Under this framework, neuron–tumor interactions may vary continuously across structural organization, neurotransmitter confinement, electrophysiological coupling, and dependence on neuronal firing dynamics. The biological determinants that position neuron–tumor interactions along this continuum remain incompletely defined. In principle, bona fide synapses would be expected to exhibit coordinated ultrastructural organization, postsynaptic scaffolding, *trans*-synaptic adhesion, and canonical forms of synaptic transmission, whereas pseudo-synaptic interfaces may display similar ultrastructural organization but differ in their physiological output, including the predominance of calcium-wave signaling and the absence of demonstrated quantal transmission, EPSP-like responses, or classical synaptic plasticity [11–13,19]. By contrast, broader paracrine neural regulation may occur without stable structural specialization or direct electrophysiological coupling. However, whether these features define discrete biological states or partially overlapping organizational programs across tumor contexts remains unresolved. Integrated ultrastructural, spatial, proteomic, and electrophysiological analyses will likely be required to establish mechanistically grounded criteria for classifying neuron–tumor interfaces.

This continuum framework is especially useful in peripheral malignancies, where a key unresolved issue is whether synapselike junctions operate through canonical synaptic transmission, noncanonical localized neurotransmission, or hybrid bioelectric states that combine rapid ionotropic signaling with slower modulatory programs.

Beyond direct contact: circuit-level and molecular mechanisms of neural regulation in solid tumors

Neural regulation in solid tumors extends beyond direct neuron–tumor interfaces to include distributed neural circuits and soluble mediators acting within the tumor microenvironment. Accordingly, tumor behavior may be shaped not only by local neuron–tumor contacts but also by circuit-level organization and diffusible signaling mechanisms operating across multiple anatomical sites. At the opposite end of this communication continuum are neural regulatory mechanisms that influence tumors without direct structural neuron–tumor coupling.

Circuit-level neural regulation

Neural regulation of solid tumors is not confined to direct neuron–tumor interfaces but can also arise from higher-order neural circuits acting upstream of the tumor microenvironment. In this context, tumor behavior is influenced not only by local nerve–tumor contacts but also by neuronal activity organized across distributed neural networks (Figure 2A).

In colorectal cancer, a polysynaptic septo-enteric circuit has been shown to increase intratumoral GABA levels and promote tumor growth through ε-subunit-containing $GABA_A$ receptors on cancer cells, despite the absence of classical synaptic contacts or detectable postsynaptic currents in tumor cells [29]. These findings demonstrate that circuit-driven neural regulation can influence tumor behavior without requiring a bona fide synaptic junction at the tumor interface.

A related but more anatomically distributed mechanism has been described in lung adenocarcinoma, where tumors engage a bidirectional tumor–brain circuit involving vagal sensory afferents and central autonomic output [30]. In this model, tumor-derived signals activate sensory pathways that relay to the brainstem, leading to increased sympathetic signaling within the tumor microenvironment. This afferent–efferent loop suppresses antitumor immunity through β2-adrenergic signaling in alveolar macrophages and promotes tumor growth. More broadly, these observations indicate that neural regulation of cancer may arise through higher-order circuit organization integrating peripheral and central neural activity, rather than through direct structural coupling between neurons and tumor cells alone. The gastric cancer setting further suggests that these interactions are bidirectional: sensory neuronal excitation evokes calcium responses in cancer cells, while cancer-cell depolarization can trigger calcium responses in sensory ganglia,

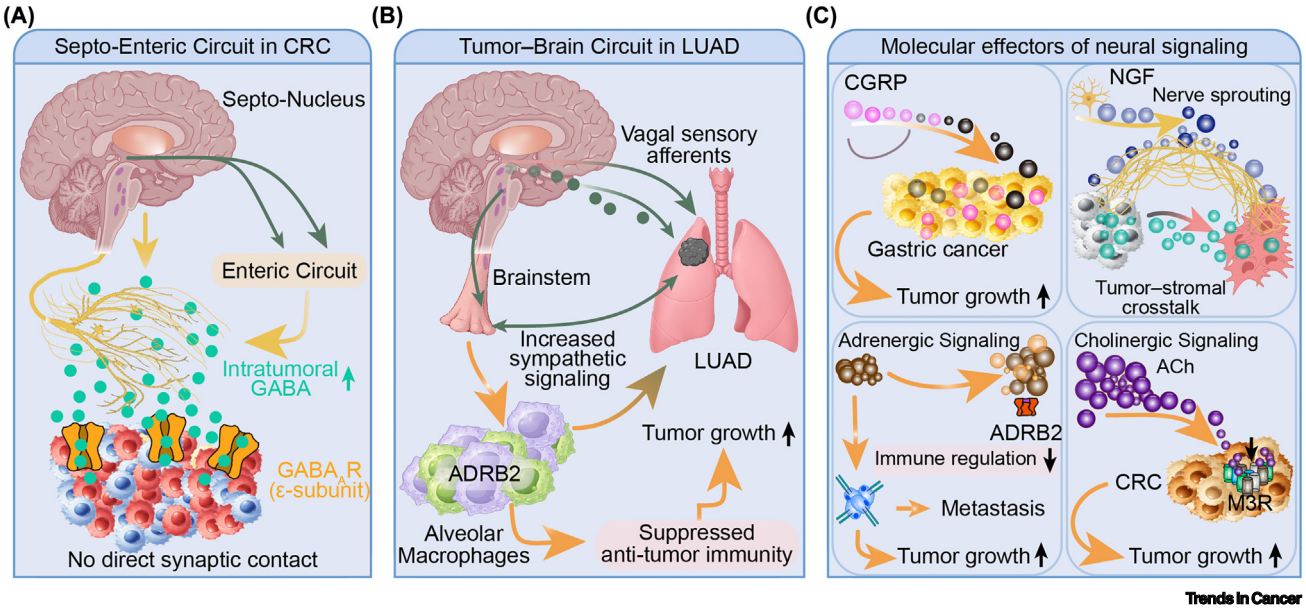

Figure 2. Circuit-level and molecular mechanisms of neural regulation in solid tumors. (A) Septo-enteric circuit in colorectal cancer. A polysynaptic septo-enteric circuit increases intratumoral γ-aminobutyric acid (GABA) levels, promoting tumor growth via ε-subunit-containing γ-aminobutyric acid type A receptor ($GABA_AR$) on cancer cells, in the absence of direct synaptic contact. (B) Tumor–brain circuit in lung adenocarcinoma. Tumor-derived signals activate vagal sensory afferents that relay to the brainstem, enhancing sympathetic output to the tumor microenvironment. β_2 adrenoreceptor (ADRB2) signaling in alveolar macrophages suppresses antitumor immunity, thereby promoting tumor growth. (C) Molecular effectors of neural signaling. Soluble, diffusible factors in the microenvironment act independently of direct electrochemical coupling. Calcitonin gene-related peptide (CGRP) promotes gastric tumor growth; nerve growth factor (NGF) drives nerve remodeling and tumor–stromal crosstalk; adrenergic signaling (via ADRB2) regulates metastasis and immune responses; and cholinergic signaling, through acetylcholine (ACh) acting on muscarinic acetylcholine receptor 3 (M3R), promotes colorectal tumor growth. CRC: colorectal cancer; LUAD: lung adenocarcinoma. Parts of the figure created using BioRender (https://BioRender.com).

raising the possibility that some tumors do not merely receive neural input but actively participate in pathological feedback circuits.

Molecular effectors of neural signaling

In parallel with circuit-level mechanisms, neuronal influence on tumors can also be mediated through soluble factors that act independently of direct electrochemical coupling. These include neurotransmitters, neuropeptides, and neurotrophic factors, which contribute to shaping tumor and stromal cell behavior within the microenvironment (Figure 2B).

Neuropeptide signaling represents one such mechanism. In gastric cancer, sensory neuron-derived calcitonin gene-related peptide (CGRP) has been shown to promote tumor growth, indicating a role for neuropeptide-dependent signaling in tumor progression [20]. Neurotrophic pathways, including nerve growth factor (NGF) signaling, further contribute to tumor progression by promoting nerve remodeling and reinforcing tumor–neural and tumor–stromal crosstalk [31,32]. Moreover, sensory neuron-derived neuropeptide signaling can modulate cancer immunosurveillance in ways that promote tumor progression, suggesting that neural regulation may extend beyond direct tumor-cell-autonomous mechanisms [7].

Parallel mechanisms operate through autonomic pathways. Adrenergic signaling links sympathetic neural activity to tumor progression, metastatic dissemination, and immune regulation, consistent with foundational studies implicating autonomic and stress-associated β-adrenergic signaling across multiple cancer contexts [33–37]. In contrast, cholinergic signaling can promote colorectal tumor growth through muscarinic receptor-dependent programs [38]. Similar neural mechanisms have also been implicated in prostate cancer, breast cancer, and head and neck squamous cell carcinoma, where perineural invasion, neuroimmune remodeling, or metastasis-associated neural interactions are associated with adverse clinical outcomes [35,37,39,40]. However, unlike gliomas and selected peripheral tumor contexts with pseudo-synaptic features, definitive evidence for bona fide synaptic or pseudo-synaptic neuron–tumor interfaces in these cancers remains limited. Collectively, these observations suggest that neural regulation of cancer involves a broader effector network in which neuropeptides, neurotrophin-dependent remodeling, and autonomic transmitters act alongside or independently of direct electrochemical communication at neuron–tumor interfaces.

Functional consequences of neural input and unresolved principles of neuron–tumor communication

Across recent studies, neural input has been increasingly linked to multiple aspects of tumor biology, including proliferation, invasion, metastasis, cellular plasticity, metabolic adaptation, and therapeutic adaptation [18,19,21,24,25,39,41]. Rather than functioning solely as trophic growth signals, neural cues increasingly appear to influence tumor-cell state and behavior at multiple levels, ranging from rapid electrophysiological responses to broader transcriptional and phenotypic adaptation. These observations suggest that neural activity may represent an additional layer of microenvironmental regulation capable of integrating electrical, biochemical, and metabolic inputs into tumor evolution.

A recurring theme across diverse tumor contexts is the convergence of neural signaling onto calcium-dependent regulatory programs. In gliomas, synaptic glutamatergic input drives membrane depolarization and calcium influx through AMPA receptor-dependent mechanisms [10,11]. Similar calcium-associated signaling responses have been described in peripheral pseudo-synaptic settings, including PDAC and gastric cancer [19,20]. Beyond acute electrophysiological responses, accumulating evidence suggests that calcium signaling may link

neuronal activity to longer-term changes in tumor-cell state. Neural input has been associated with programs related to neuronal mimicry, lineage plasticity, and adaptive cellular state transitions [18,21,22]. However, the mechanistic pathways connecting synaptic activity to durable epigenetic or transcriptional reprogramming remain incompletely defined. Mechanistically, activity-dependent calcium influx may couple neural signaling to downstream transcriptional regulation through calcium-sensitive signaling programs; however, whether such pathways directly mediate durable epigenetic reprogramming or stable tumor-cell state transitions in neuron-associated tumor populations remains unresolved.

These unresolved electrophysiological properties are also directly relevant to the definitional distinction between bona fide synapses and pseudo-synaptic interfaces. Although pseudo-synaptic interfaces can mediate robust localized calcium influx, calcium-wave propagation, and neurotransmitter-responsive signaling, it remains unknown whether these interactions exhibit the defining physiological hallmarks of canonical synapses, including quantal transmission, characteristic EPSP/IPSP kinetics, action-potential-coupled responses, and activity-dependent synaptic plasticity. These observations raise the possibility that neuron–tumor communication may contribute not only to tumor growth but also to tumor-cell plasticity and therapeutic resistance. Neural activity may enable subsets of tumor cells to adopt stress-adapted or neuronal-like phenotypes that support survival under selective pressure. At present, however, it remains unclear whether such effects occur broadly across tumor populations or are restricted to specialized neural niche-associated subpopulations. Similarly unresolved is whether distinct modes of neuron–tumor communication—including bona fide synapses, pseudo-synaptic interfaces, and circuit-level neural regulation—converge on shared downstream programs or instead generate context-dependent functional states across different tumor types.

Emerging evidence further suggests that neural regulation intersects with metabolic adaptation. Localized neural niches may provide tumor cells with access not only to neurotransmitter-dependent signaling but also to alternative metabolic substrates capable of supporting growth under stressed conditions. Recent studies on breast cancer brain metastasis further suggest that tumor cells can actively exploit glutamate-rich neural microenvironments through increased expression of glutamate transporters, enabling glutamate utilization to support oxidative phosphorylation, glycolysis, and invasive behavior [25]. These observations raise the possibility that neuron-associated microenvironments may function not only as signaling hubs but also as specialized metabolic niches that provide selective advantages during tumor progression and metastatic adaptation. One possible mechanism underlying these adaptations is localized access to neurotransmitter-associated metabolic substrates within neural niches. Glutamate-rich microenvironments may support metabolic adaptation under stressed conditions, although the precise metabolic pathways and their functional importance across tumor contexts remain incompletely defined.

The interaction between neural signaling and tumor immunity remains an important unresolved area of cancer neuroscience. Neural activity can influence antitumor immunity through multiple mechanisms, including adrenergic regulation of immune populations and neuropeptide-dependent modulation of inflammatory responses [7,30,33]. Furthermore, recent studies suggest that cancer-induced nerve injury programs may contribute to immunosuppressive remodeling and resistance to immune checkpoint blockade [42,43]. Cancer-induced nerve injury may represent a distinct neuroimmune mechanism rather than a simple consequence of tumor-associated innervation. Baruch *et al*. [43] showed that cancer cells can damage tumor-associated nerves through myelin degradation, leading injured neurons to activate injury programs associated with activating transcription factor 3 (ATF3), as well as interleukin-6 (IL-6)- and type I interferon-mediated inflammatory signaling. As nerve injury accumulates during

tumor progression, this initially regenerative inflammatory response may become chronic and contribute to a suppressive immune tone characterized by immunosuppressive macrophage states, exhausted $CD8^+$ T cells, and reduced responsiveness to anti-programmed cell death protein 1 (PD-1) therapy. Importantly, these findings further suggest that tumor-associated nerves can regulate immunity not only through neurotransmitter or neuropeptide signaling but also through injury-induced neuroinflammatory programs.

These observations raise the possibility that neural signaling regulates not only tumor-cell-intrinsic programs but also broader immune states within the tumor microenvironment. However, the relative contributions of tumor cells, stromal populations, and immune compartments to these effects remain poorly resolved. At a more basic neurobiological level, it remains unresolved whether peripheral neuron–tumor contacts are chemical, electrical, or mixed in nature; whether they generate action-potential-coupled EPSP-like depolarizations, graded calcium waves, or other noncanonical electrophysiological states; and whether these responses are transient, sustained, plastic, or reversible with repeated stimulation. Addressing these issues will require direct electrophysiological interrogation, including patch-clamp approaches adapted to tumor–nerve coculture and *in situ* preparations.

Defining the conditions under which neural input drives proliferation, promotes plasticity, or alters immune responses will be important for clarifying the biological significance of tumor innervation. More broadly, distinguishing causal neural dependencies from associations between tumor growth and nerve presence remains a central challenge for the field. A related conceptual question is why tumors would require highly localized synapselike signaling at all if paracrine signaling alone were sufficient. One possibility is that synapselike junctions provide speed, specificity, high local neurotransmitter concentrations, and coupling to neuronal firing patterns, thereby allowing tumors to decode dynamic neural activity rather than simply respond to tonic ligand exposure. Conversely, broader paracrine signaling may support slower, longer-range, or more tonic trophic regulation. These different modes of neuron–tumor communication may therefore help distinguish tumor states, grades, or metastatic behaviors.

Additional unresolved questions concern cellular scope and stability. It remains unknown whether peripheral nerves form comparable synaptic or synapselike contacts with nonmalignant stromal populations such as fibroblasts, immune cells, or epithelial progenitors, and whether the assemblies observed in tumors are stable long-lived structures or reversible activity-induced junctions. A more complete molecular inventory of these interfaces is also lacking, despite the recurrent implication of glutamate receptors and other postsynaptic signaling components across both central and peripheral tumor settings. Together, these unresolved questions highlight that the field still lacks a unified framework for defining, classifying, and functionally interpreting neuron–tumor interactions across different anatomical and disease contexts. Another limitation is that many mechanistic *in vivo* studies have relied predominantly on male rodent models. Whether neuron–tumor interactions vary across sex, hormonal context, developmental stage, or species remains largely unknown. Resolving these issues will be essential for distinguishing causal neural dependencies from correlative tumor-associated innervation and for determining when neural signaling represents a therapeutically actionable vulnerability in cancer.

Therapeutic opportunities and future directions

The recognition that tumors engage the nervous system through diverse organizational states, ranging from bona fide synapses to pseudo-synaptic interfaces and circuit-level regulation, raises the possibility that neural signaling may represent a therapeutically actionable dimension of tumor biology. However, the heterogeneity of neuron–tumor communication across anatomical

contexts also suggests that distinct therapeutic strategies may be required for different forms of neural dependency.

Current approaches targeting neural regulation in cancer span multiple mechanistic levels, including inhibition of neurotransmitter signaling, disruption of neuron–tumor interactions, modulation of autonomic pathways, and interference with neural niche-associated adaptation programs. In gliomas and other synaptically integrated tumors, glutamatergic signaling pathways represent a potential therapeutic vulnerability [10,11,18,19]. Conversely, tumors regulated predominantly through broader circuit-level or autonomic mechanisms may be more susceptible to interventions targeting adrenergic signaling or neuroimmune pathways [30,33]. Emerging studies further suggest that neural niche-associated metabolic adaptation and immunosuppressive remodeling may themselves become therapeutically targetable states [25,43]. In principle, this therapeutic space may also extend to interventions that reduce pathological neuronal hyperexcitability or disrupt tumor-to-nerve feedback, particularly in settings where cancer cells appear to participate in bidirectional neurobiological loops.

Despite these advances, several conceptual and translational questions remain unresolved (see Outstanding questions). A central issue is what defines a true neuron–tumor synapse in peripheral cancers. Although synapselike interfaces have been identified in PDAC and other extracranial tumors, it remains unclear whether these structures fully satisfy the electrophysiological criteria of bona fide synapses or instead represent distinct hybrid neuro-effector junctions with noncanonical signaling properties. Resolving this distinction will be important not only for terminology but also for determining whether therapies should target classical synaptic machinery, localized neurotransmitter signaling, or broader neural microenvironmental interactions.

Another unresolved question is whether neural dependencies are intrinsic properties of tumor subclones or are acquired dynamically within neural niches during tumor evolution. If responsiveness to neuronal input reflects a reversible adaptive state rather than a fixed lineage property, therapeutic vulnerabilities may differ substantially across tumor stages, metastatic sites, or treatment contexts. Similarly, it remains uncertain whether synaptic, pseudo-synaptic, neuropeptidergic, and circuit-level inputs converge on shared downstream programs—including calcium signaling, plasticity, metabolism, and immune remodeling—or instead generate distinct context-dependent phenotypes across tumor types.

These unresolved biological questions directly influence how neural dependencies can be identified and therapeutically targeted in patients. Future studies will need to establish biomarkers capable of distinguishing tumors driven by localized neuron–tumor interfaces from those regulated predominantly through broader circuit-level or paracrine neural mechanisms. More precise electrophysiological, ultrastructural, spatial-transcriptomic, and functional mapping approaches will likely be required to define clinically actionable forms of neuron–tumor communication across different cancers. Systematic correlative light and electron microscopy, combined with functional readouts, should be especially valuable for determining when the term ‘synapse’ is biologically and ultrastructurally justified in peripheral tumors and when a more precise terminology, such as pseudo-synapse or localized neuro-effector junction, is warranted.

More broadly, understanding how tumors integrate neural signaling into programs governing plasticity, metastasis, metabolism, and immune regulation may ultimately reshape current models of tumor ecology. Rather than representing passive stromal components, nerves may function as dynamic regulators of tumor state and adaptation across multiple stages of cancer progression. Defining when these neural interactions represent causal dependencies rather than secondary

consequences of tumor growth will be central to translating cancer neuroscience into clinically effective therapeutic strategies. From a broader biological perspective, tumor innervation may reflect pathological co-option of conserved neural programs involved in tissue homeostasis, regeneration, wound repair, and neuroimmune regulation, as peripheral nerves normally participate in tissue maintenance, epithelial repair, and inflammatory control during injury responses [44–47]. In this view, neuron–tumor interfaces may represent an adaptive hijacking of normal peripheral and central neurobiology rather than an entirely novel cancer-specific invention.

Concluding remarks

Neuron–tumor communication is increasingly recognized as an organizational dimension of the tumor ecosystem that spans a continuum from bona fide synapses to pseudo-synaptic and circuit-level neural interactions. Defining the structural and functional principles governing these states will be essential for distinguishing causal neural dependencies from correlative tumor-associated innervation. As the field advances, integrated structural, electrophysiological, spatial, and functional approaches should help clarify how tumors exploit neural programs during progression and identify clinically actionable neural vulnerabilities across cancer contexts.

Outstanding questions

What defines a true neuron–tumor synapse in peripheral cancers?

Do neuron–tumor contacts outside the central nervous system meet ultrastructural and functional criteria of bona fide synapses, or do they represent distinct hybrid neuro-effector junctions with noncanonical signaling properties?

Are neural dependencies intrinsic or acquired within tumor ecosystems?

Is responsiveness to neuronal input a pre-existing feature of specific tumor subclones, or is it induced by exposure to neural niches and microenvironmental cues during tumor evolution?

Do diverse modes of neural signaling converge on shared tumor programs?

How do synaptic, pseudo-synaptic, neuropeptidergic, and circuit-level inputs integrate at the molecular level, and do they drive common downstream processes (e.g., calcium signaling, plasticity, and metabolism) or context-specific phenotypes?

Which tumors are therapeutically vulnerable to targeting neural signaling?

How can neural dependencies be identified in patients, and will effective therapies require disrupting local neuron–tumor interfaces, broader neural circuits, or tumor adaptations to neural niches?

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Declaration of interests

The authors declare no conflict of interests.

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