Chen *et al. Int Open Med J.* 2026;1:191-226
DOI: 10.65364/iomj.2026.11

International Open Medical Journal

Review

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The gut-neuro-tumor signaling feedback driving dynamic remodeling of the tumor microenvironment: a review

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How to cite this article: Chen Y, Wang X. The gut-neuro-tumor signaling feedback driving dynamic remodeling of the tumor microenvironment: a review. *Int Open Med J.* 2026;1:191-226. https://dx.doi.org/10.65364/iomj.2026.11

Received: 9 Jun 2026 **Accepted:** 23 Jul 2026 **Published:** 31 Aug 2026

Abstract

Historically, research on the tumor microenvironment (TME) has focused primarily on local cellular interactions. Evidence now indicates that the gut microbiota and nervous system can each influence tumor biology and can interact bidirectionally with host immune and metabolic pathways. The gut microbiota generates neuroactive products, including short-chain fatty acids (SCFAs) and tryptophan metabolites, and individual studies support microbiota-to-neural signaling, neural regulation of tumor or immune-cell behavior, and tumor-associated changes in neural and intestinal homeostasis. On the basis of these convergent but largely compartmentalized observations, we propose a gut-neuro-tumor signaling feedback framework in which the nervous system may, in selected contexts, integrate or redistribute microbiota-derived signals toward the tumor microenvironment (TME). The complete hierarchical sequence has not been demonstrated within a single experimental system, and microbiota-derived factors may also affect tumors through neural-independent circulatory or immune routes. Tumors may contribute to feedback through local neural remodeling and systemic stress responses, whereas translocated gut microorganisms can directly affect selected tumors. This review evaluates the evidence supporting each component, distinguishes experimentally supported interactions from integrative hypotheses, and outlines strategies required to test the proposed framework. Its therapeutic implications should currently be regarded as investigational and context dependent rather than as those of an established druggable circuit.

Keywords: Gut-brain axis, intratumoral microbes, gut microbes, nervous system, tumor microenvironment

INTRODUCTION

Cancer progression is no longer viewed as a tumor cell-intrinsic process but rather as an emergent property of a highly dynamic and multi-layered TME, in which immune, stromal, metabolic, and microbial components interact across spatial and temporal scales[1-4]. While early paradigms emphasized local cellular crosstalk within the TME, accumulating evidence has expanded this view toward a system-level regulatory network, wherein distal organs and physiological systems actively participate in shaping tumor behavior. Among these, two regulatory axes have attracted increasing attention, the gut microbiota and the nervous system. The gut microbiome has been established as a critical modulator of tumorigenesis and therapeutic response through its capacity to generate bioactive metabolites, regulate systemic immunity, and influence host metabolism[5-7]. In parallel, the nervous system has emerged as a functional component of the TME, capable of directly promoting tumor growth, invasion, and immune evasion via neurotransmitters, neurotrophic factors, and electrophysiological signaling[8-11]. These advances have given rise to the rapidly evolving fields of tumor microbiomics and cancer neuroscience. However, despite substantial progress, current researches and most existing reviews largely conceptualize these systems as parallel or loosely coupled regulators of tumor biology. This fragmented perspective overlooks the fundamental question of how microbiota-derived signals are hierarchically integrated, spatially coordinated, and dynamically propagated to influence tumor progression at the systems level. In particular, the mechanistic role of the nervous system as an intermediary that translates microbial cues into structured tumor-regulatory programs remains insufficiently defined. Moreover, emerging data suggest that tumors are not passive recipients of systemic inputs. Instead, they actively remodel neural architecture, perturb gut homeostasis, and induce systemic feedback responses, thereby establishing a bidirectional and potentially self-reinforcing regulatory loop[12-15]. This raises critical unresolved issues, including whether neural activity acts as a driver or consequence of tumor progression, how context-dependent effects of neurotransmitters and microbial metabolites arise, and why targeting individual pathways often yields limited therapeutic efficacy. The proposed framework is conceptually distinct from, but complementary to, several established models. The gut-brain axis primarily describes bidirectional communication between the intestinal ecosystem and the nervous system, usually without incorporating the tumor as an active regulatory node. The gut-tumor axis focuses on direct microbial, metabolic, and immune effects on tumor biology but generally does not define the nervous system as an intermediary that processes and spatially coordinates microbiota-derived signals. Cancer neuroscience examines reciprocal interactions between neural elements and tumor cells, whereas microbiota-derived inputs and tumor-induced disruption of intestinal homeostasis are not usually central components. Similarly, neuroimmune-tumor models emphasize neural regulation of immune cells within the TME but do not generally close the feedback loop through the gut microbiota.

As illustrated in Figure 1, the novelty of the proposed gut-neuro-tumor signaling feedback lies not in claiming that its individual pathways are newly discovered, but in organizing separately supported interactions into a testable closed-loop architecture. In this working model, the gut microbiota is considered a source of metabolic and immunological inputs, the nervous system is hypothesized to sense, filter, integrate, or redistribute a subset of these inputs, and the TME represents a context-dependent response compartment. Tumors are further proposed to provide feedback by remodeling neural structures, activating neuroendocrine stress pathways, and perturbing intestinal or microbial homeostasis. These assignments are conceptual and should not be interpreted as universally established functions. Direct evidence currently supports several component interactions, including microbiota-dependent modulation of neural activity, neural regulation of tumor or immune-cell behavior, and tumor-associated changes in neural or intestinal physiology. By contrast, direct evidence for the complete sequence of microbiota-derived input, neural integration or amplification, TME remodeling, and tumor-driven feedback within the same experimental system is lacking. Moreover, microbial metabolites and immune mediators can reach tumors without obligatory neural processing. Accordingly, the proposed integrator and amplifier functions

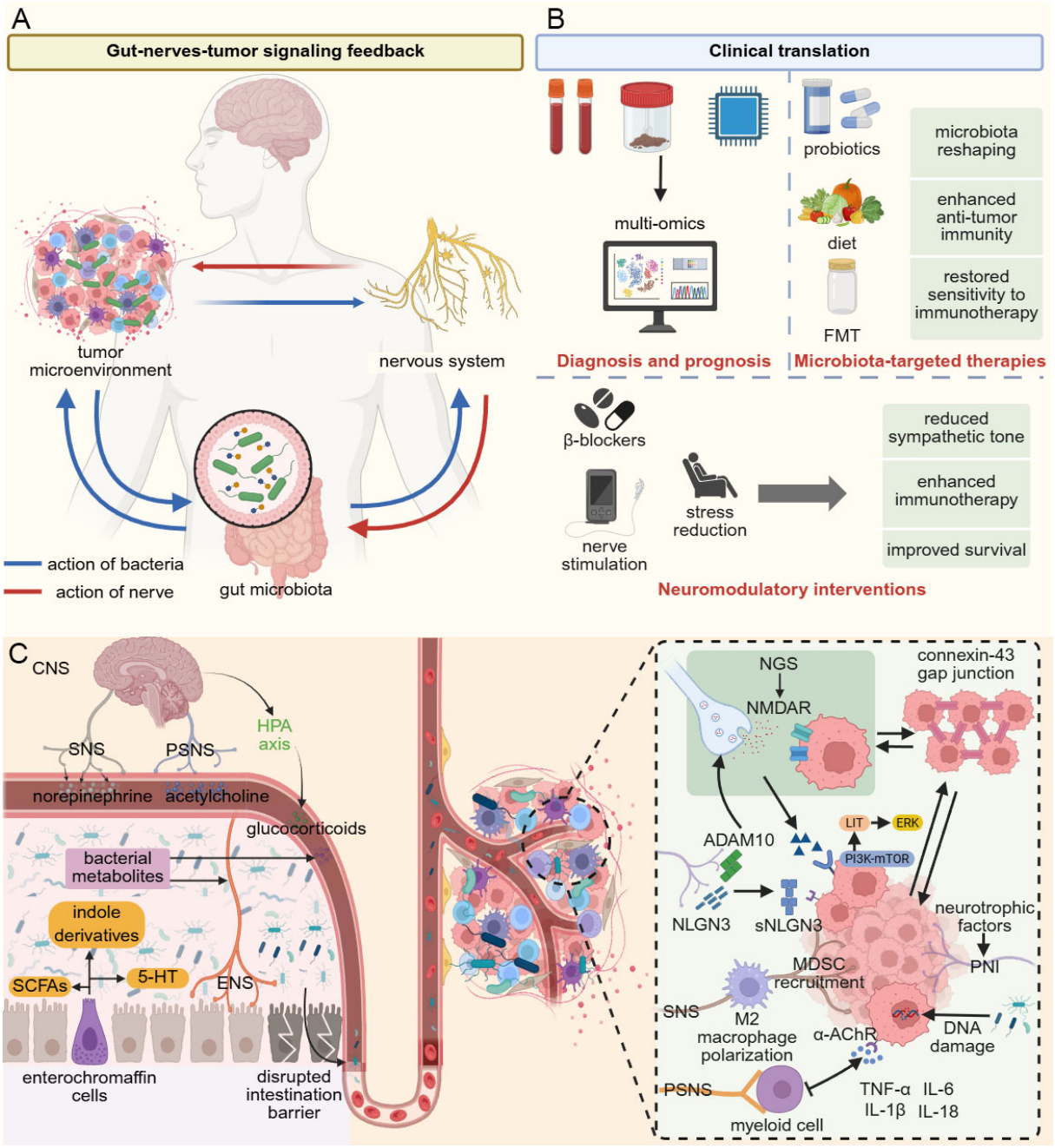

Figure 1. Schematic diagram of the mechanisms by which the gut-neuro-tumor signaling feedback functions in the integration of multiple. FMT: faecal microbiota transplantation; CNS: central nervous system; SNS: sympathetic nervous system; PSNS: parasympathetic nervous system; SCFA: short-chain fatty acid; 5-HT: 5-hydroxytryptamine; ENS: enteric nervous system; NGS: neuron-to-glioma synapses; NMDAR: N-methyl-D-aspartate receptor; ADAM10: a disintegrin and metalloproteinase domain-containing protein 10; NLGN3: neuroligin-3; TNF-α: tumor necrosis factor-α; TILs: tumor-infiltrating lymphocytes; ERK: extracellular signal-regulated kinase; PI3K-mTOR: phosphoinositide 3-kinase-mechanistic target of rapamycin signaling pathway; PNI: perineural invasion; IL-6: interleukin-6; IL-18: interleukin-18; α-AChR: α-acetylcholine receptor.

of the nervous system are treated throughout this review as testable hypotheses derived from convergent evidence. We therefore distinguish directly demonstrated mechanisms, indirect evidence for neural mediation, and predictions that require causal validation.

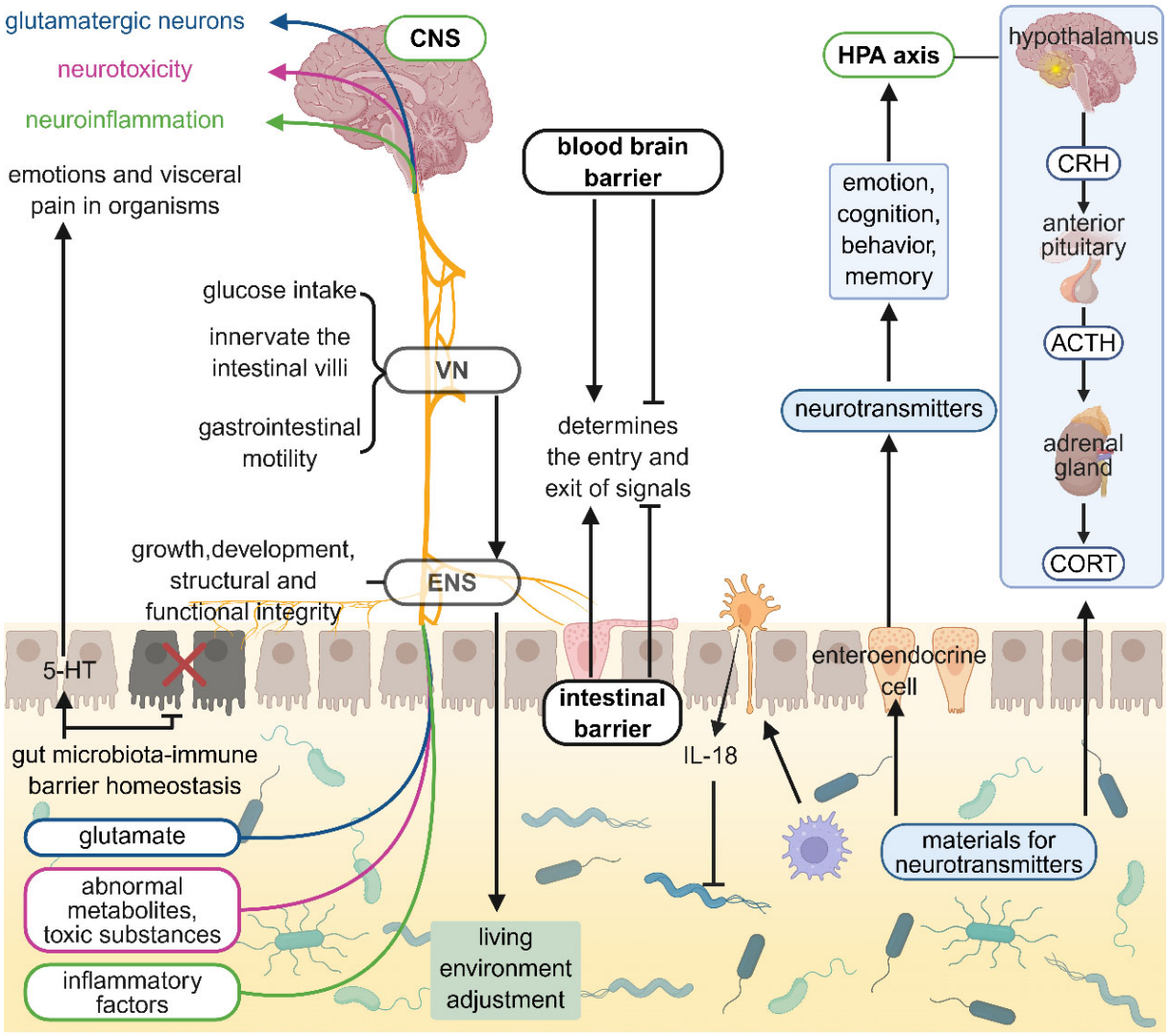

Figure 2. Schematic diagram of the mechanisms by which the gut-brain axis functions in the integration of multiple microbiota, neural and immune pathways. This figure illustrates the bidirectional communication network between the gut microbiota and the CNS mediated through neural, immune, and endocrine pathways. CNS: central nervous system; HPA: hypothalamic-pituitary-adrenal axis; VN: vagus nerve; ENS: enteric nervous system; IL-18: interleukin-18; ACTH: adrenocorticotropic hormone; CORT: cortisol; 5-HT: 5-hydroxytryptamine.

GUT-BRAIN AXIS

Within the gut-neuro-tumor signaling feedback, the gut microbiota represents a major source of diverse biochemical and immunological signals. However, these signals do not necessarily act directly on tumors. Instead, they may first be sensed, integrated, and contextually processed by the nervous system, which subsequently determines how microbiota-derived cues are propagated throughout the host. As illustrated in Figure 2, bidirectional communication between the gut and the brain is primarily mediated through three interconnected routes: neural, immune, and neuroendocrine pathways. These pathways collectively transmit microbial, metabolic, inflammatory, and hormonal signals between the gastrointestinal tract and the central nervous system, thereby contributing to both physiological homeostasis and disease progression.

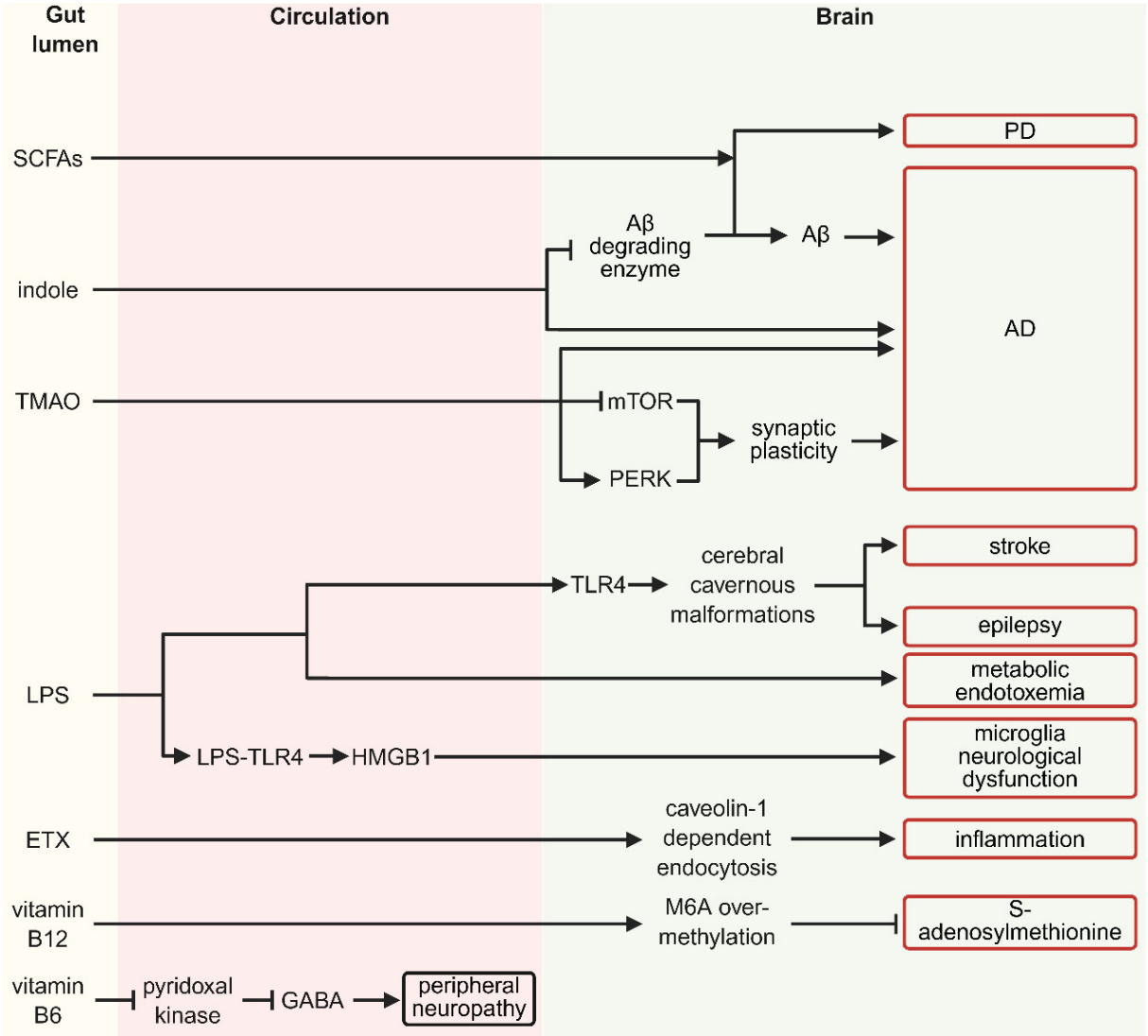

Figure 3. A schematic diagram illustrating the interactions of circulating microbial metabolites and their neuropathological effects within the gut-brain axis. This diagram summarizes the key mechanisms by which small molecules and toxic factors from gut microbiota enter the CNS via systemic circulation and modulate brain function and disease pathogenesis. SCFA: short-chain fatty acid; PD: Parkinson's disease; AD: Alzheimer's disease; TMAO: trimethylamine N-oxide; mTOR: mechanistic target of rapamycin; PERK: protein kinase R-like endoplasmic reticulum kinase; TLR4: Toll-like receptor 4; LPS: lipopolysaccharide; HMGB1: high-mobility group box 1; ETX: epsilon toxin; GABA: γ-aminobutyric acid; CNS: central nervous system.

Regulation of the gut microbiota

The gut-brain axis is a complex communication between the microbiota and neural circuits throughout the brain. This network contributes to the regulation of behavior and brain function, and is involved in the genesis and progression of various central nervous system (CNS) disorders. The commensal bacteria function by their metabolites, consisting of indoles, γ-aminobutyric acid (GABA), serotonin (5-HT), and SCFA. As Figure 3 indicates, these play a crucial role in regulating neuronal function, neurotransmitter synthesis, and in the development and progression of diseases.

Neural pathway

Vagus nerve

As the primary component of the parasympathetic nervous system, the vagus nerve (VN) constitutes the fastest and most direct anatomical pathway between the gut and the brain. However, vagal nerve endings

typically do not physically contact gut microbiota. Instead, they rely on enteroendocrine cells (EECs) and the enteric nervous system (ENS) as signal sensors to mediate indirect gut-brain communication[16]. More groundbreaking is the discovery that specific EECs can form functional synaptic structures called neuropods with neurons in the vagal nodose ganglion, utilizing neurotransmitters like glutamate to enable millisecond level rapid signal transmission to the brain[17]. Notably, tryptophan catabolites produced by gut microbiota can not only activate TRPA1 channels on EECs to trigger rapid vagal firing but also, when produced in excess, directly stimulate vagal afferent fibers and induce persistent anxiety-like behaviors[18]. Concurrently, the modulatory effects of probiotic strains on the CNS are highly dependent on the anatomical integrity of the VN[19]. Conversely, colonization by pathogenic bacteria induces abnormal expression of c-Fos protein in vagal afferent brain regions, directly triggering host anxiety like behaviors[20].

Enteric nervous system

Functioning as the intrinsic control center of the gastrointestinal tract, the ENS not only regulates gut motility, local blood flow, and epithelial secretion but also serves as a fundamental interface connecting the intestinal microenvironment with the host physiological state. Notably, the structural integrity and functional maturation of the ENS are highly dependent on the early colonization and continuous signaling input from the gut microbiota[21]. During the critical postnatal developmental window, microbiota activate Toll-like receptor signaling pathways, directly driving the survival and differentiation of enteric neurons as well as the recruitment of glial cells[22]. Furthermore, microbial metabolites act as signaling molecules to induce enterochromaffin cells to release 5-HT[23]. This subsequently activates specific receptors on the ENS to precisely maintain gut peristaltic rhythms[24].

Autonomic nervous system

Within the complex network of gut and brain communication, the Autonomic Nervous System (ANS), through the dynamic equilibrium between the sympathetic and parasympathetic branches, plays an indispensable role in maintaining intestinal physiological homeostasis and systemic metabolic balance. In contrast to the immediate modulation mediated by the VN, the gut microbiota and their metabolites constitute a more profound, inter organ physiological feedback loop by regulating sympathetic nervous activity. Notably, microbiota derived SCFAs have been identified as key signaling molecules that activate the sympathetic pathway[25]. This feedback mechanism, linking the gut microenvironment to sympathetic nerve endings, ensures the host's rapid stress response and adaptation to environmental changes under various pathophysiological conditions[26]. The microbiota driven regulation of the sympathetic nervous system (SNS) is particularly prominent in the precise control of glucose homeostasis[27]. Studies have shown that the gut microbiota, by influencing metabolite sensing in the portal vein system, triggers a sophisticated gut-brain-liver neuroreflex arc[27]. This nonhormone dependent metabolic regulation reveals how the gut microbiota utilizes the ANS as a frequency modulator to intervene in the host's energy metabolism across space and time[28].

Microbial metabolites

The gut microbiota, functioning as a highly active metabolic hub, continuously generates a series of neuroactive metabolites through the fermentation of dietary fibers and the transformation of endogenous substances. These metabolites thus serve as pivotal messengers in gut-brain communication. Within this intricate metabolic network, SCFAs, primarily acetate, propionate, and butyrate, are core lipid metabolites produced via anaerobic fermentation of dietary fibers[29]. As these metabolites enter the systemic circulation and reach the CNS, SCFAs demonstrate multifaceted roles. They not only effectively promote neurogenesis and contribute to the establishment of systemic immune barriers but also function as natural HDAC inhibitors[30]. By means of epigenetic modifications, they significantly ameliorate host cognitive function and alleviate neuroinflammation[31,32]. Corresponding to the fermentation of carbohydrates, the microbial

Table 1. Summary of main neurotransmitters between gut bacteria and nervous system

Neurotransmitter	Chemical formula	Metabolic pathway	Bacterial strain	Experimental model
GABA	$C_4H_9NO_2$	glutamate metabolism	*Bifidobacterium*, *Bacteroides fragilis*, *Parabacteroides*, *Eubacterium*;	BALB/c mice treated with *L. rhamnosus* probiotics;
norepinephrine	$C_8H_{11}NO_3$	tyrosine and phenylalanine metabolism	*Bacillus mycoides*, *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, *Serratia marcescens*;	GF and SPF BALB/c mice, BALB/c mice monocolonized with *E. coli*;
5-HT	$C_{10}H_{12}N_2O$	tryptophan metabolism	*Escherichia coli*, *Hafnia alvei*, *Klebsiella pneumoniae*, *Lactobacillus plantarum*, *Lactococcus lactis subsp.cremoris*, *Morganella morganii*, *Streptococcus thermophilus*;	lactobacillus and streptococcus cultures;
dopamine	$C_8H_{11}NO_2$	tyrosine and phenylalanine metabolism	*Bacillus cereus*, *Bacillus mycoides*, *Bacillus subtilis*, *Escherichia coli*, *Hafnia alvei*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus vulgaris*, *Serratia marcescens*, *Staphylococcus aureus*;	GF and SPF BALB/c mice, BALB/c mice monocolonized with *E. coli*;
histamine	$C_5H_9N_3$	phenylalanine and histidine metabolism	*Citrobacter freundii*, *Enterobacter species*, *Hafnia alvei*, *Klebsiella pneumoniae*, *Lactobacillus plantarum*, *Lactobacillus hilgardii*, *Lactobacillus mali*, *Lactococcus lactis subsp.cremoris*, *Lactococcus lactis subsp.lactis*, *Morganella morganii*, *Oenococcus oeni*, *Pediococcus parvulus*, *Streptococcus thermophiles*;	C57BL/6 mice monocolonized with *M. morganii*, HEK293 cell;

GABA: γ-aminobutyric acid; BALB/c: BALB/c mouse strain; GF: germ-free; SPF: specific pathogen-free; 5-HT: 5-hydroxytryptamine.

metabolism of amino acids constitutes another critical axis of the gut-brain pathway. Upon crossing the blood-brain barrier (BBB), these molecules finely tune the activation state of astrocytes by binding to and activating AHR, thereby exerting profound anti-inflammatory and neuroprotective effects[33]. On the other hand, trimethylamine N-oxide (TMAO), derived from dietary choline metabolism, exhibits a concentration-dependent double-edged sword effect in neuroregulation. Under physiological concentrations, TMAO helps maintain the structural integrity of the BBB, which is crucial for restricting the invasion of peripheral pro-inflammatory factors into the brain[34,35]. However, when microbial metabolic dysregulation leads to the pathological accumulation of TMAO, it not only induces severe neuroinflammation but also disrupts synaptic plasticity, ultimately resulting in cognitive impairment[36]. These intertwined metabolic pathways collectively constitute the biochemical foundation through which the gut microenvironment systematically reshapes central nervous function and local immune status.

The role of the nervous system

As shown in Table 1, in the bidirectional communication of the gut-brain axis, the nervous system not only receives signals from the gut but also exerts profound regulatory effects on the composition, distribution, and metabolism of the gut microbiota through multiple pathways. This top and down regulation is primarily mediated via neural, endocrine, and immune circuits.

Direct and indirect regulation of the ENS

The ENS, owing to its extensive and highly autonomous neuronal network, is regarded as the most direct interface for the host's top and down regulation of the gut microbiota. Although ENS neurons do not physically extend into the gut lumen to make direct contact with microbes, they exert profound indirect influences through a sophisticated network of chemical signaling. Specifically, ENS neurons synthesize and release over 30 neurotransmitters, neuropeptides, and neurotrophic factors, including Acetylcholine (Ach), catecholamines, 5-HT, and histamine[37]. These abundant neural signals not only regulate gut motility, local blood flow, and epithelial secretion but also reshape the local mucosal microenvironment by altering its physicochemical properties[38]. This, in turn, acts as an environmental selection pressure that indirectly

modulates the community composition and metabolic activity of the gut microbiota[39]. This neuro and microbial regulatory mechanism have been robustly substantiated at the multi-omics level. More importantly, this ENS-based signaling is crucial for maintaining postnatal gut development and microbial homeostasis. Specific genetic knockout or deficiency of choline acetyltransferase in enteric neurons leads to marked motility disorders and inevitably accompanies severe dysbiosis[40]. This body of evidence strongly suggests that the signaling network of the ENS plays a pivotal hub role in maintaining host and microbe symbiosis.

Descending regulation of the ANS

Within the intricate network of gut-brain communication, the ANS, via the efferent fibers of the sympathetic and parasympathetic nerves, precisely transmits high level commands from the brain to intestinal effector cells. This process systematically reshapes the gut micro ecology at a macroscopic level. Vagal efferent fibers primarily release ACh to act upon EECs, enteric neurons, and other effector cells[41]. This efferent signaling not only fine tunes gut motility rhythms and glandular secretion but also reflexively screens and restructures the microbial community composition by altering the physicochemical environment within the gut[42,43]. In parallel with the protective and secretory promoting roles of the vagus nerve, the SNS provides a counter regulatory mechanism for physiological and immune modulation. Sympathetic nerve endings, originating from prevertebral ganglia, primarily release catecholaminergic neurotransmitters such as norepinephrine (NE) into the gut wall[44]. When sympathetic tone increases, NE binds to adrenergic receptors, directly inhibiting gut motility and mucosal secretion while triggering local microvascular constriction[45]. This leads to a significant reduction in tissue perfusion. This mediated drastic decline in hemodynamics and gut motility profoundly alters the intraluminal oxygen gradients, pH levels, and nutrient availability[46]. Acting as a potent environmental selection pressure, it indirectly but strongly determines the survival and colonization advantages of different bacterial taxa[47]. Therefore, the dynamic interplay between sympathetic and parasympathetic efferent signals within the autonomic nervous system dictates the physical and biochemical characteristics of the gut microenvironment by regulating blood flow and inflammatory responses.

THE NERVOUS SYSTEM AND TUMOR

Building upon microbiota-driven neural reprogramming, the next critical step of the gut-neuro-tumor signaling feedback lies in how neural outputs are spatially delivered to the TME. Tumors are not passive recipients of neural signals. Instead, they actively exploit neural innervation to coordinate immune suppression, metabolic adaptation, and invasive behavior. As shown in Table 2, a growing body of research indicates that nerve-tumor interactions are a key mechanism driving tumor progression. Selected tumor types can sense and respond to neuronal activity. Functional neuron-tumor synaptic interactions have been demonstrated most clearly in glioma and selected brain-metastasis models, whereas extracranial tumors more commonly interact with nerves through neurotransmitters, neuropeptides, neurotrophic factors, Schwann cells, and perineural invasion. Neurotransmitters released by neurons can promote the proliferation, migration, and invasion of tumor. Furthermore, neuronal activity itself can significantly accelerate tumor growth. In addition to neurons, astrocytes, microglia, and immune cells in the TME collectively construct a multicellular, synergistic protumor network that promotes tumor growth and spread. Therefore, nerve and tumor interactions are not only a crucial mechanism for tumor progression but also provide potential therapeutic targets for novel treatment strategies. Importantly, neural regulation is highly dependent on tumor type and anatomical context. Direct electrochemical coupling through functional neuron-tumor synapses has been most convincingly demonstrated in primary brain tumors, particularly high-grade gliomas, and in selected models of brain metastasis. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated synaptic integration, activity-dependent

Table 2. Summary of mechanisms underlying neuron and tumor interactions, including tumor types, involved signaling pathways, implicated immune cells, and associated clinical implications

Tumor	Signal pathway/cytokines	Immune cells	Mechanism	Clinical impact
prostate cancer	NGF-TrkA, CGRP-RAMP1, TRPV1, Piezo1	M2, ILC2	• Tumors secrete NGF to recruit sensory nerves, establishing a nerve and tumor feedback loop, Nerve sprouting and formation of neuroma-like structures, and TRPV1-mediated pain signaling;	• Poor prognosis, increased risk of PNI;
gastric cancer	CGRP-RAMP1/CALCRL, TRPV1, PAR2, NGF-TrkA	M2, ILC2, Treg cell	• Tumors secrete neurotrophic factors to recruit sensory nerves, Electrochemical coupling and neuropeptide release, TRPV1/PAR2-mediated neuronal sensitization;	• *Helicobacter pylori* infection exacerbates neuron and tumor interactions;
pancreatic ductal adenocarcinoma	β_2-Adrenergic-Neurotrophin loop, HGF/c-Met-mTOR/NGF axis	TAMs, MDSCs, Treg cell	• Neural reprogramming and PNI contribute to pancreatic cancer progression. Reciprocal signaling among tumor cells, peripheral nerves, and cancer-associated fibroblasts establishes a positive feedback loop, while mechanosensitive ion channels further promote invasive growth and neural infiltration;	• High intratumoral nerve density is associated with an unfavorable prognosis; • Preclinical evidence suggests that combining neural-targeted interventions with immunotherapy may improve therapeutic efficacy;
melanoma	CGRP-RAMP1, TRPV1, TGF-β	$CD8^+$ T cell, M2, MDSCs	• CGRP induces $CD8^+$ T cell exhaustion, neuron and immune interactions promote immunosuppression and nerve repair-like responses support tumor growth;	• Targeting CGRP or TRPV1 can enhance the efficacy of immunotherapy;
oral cancer	CGRP-RAMP1, SP-NK1R, A2A, TNF-α	$CD8^+$ T cell, NK, M2	• tumor-secreted TNF-α/adenosine activates sensory nerves and CGRP suppresses anti-tumor immunity;	• Aggressive progression, poor prognosis;
high-grade glioma	AMPAR-mediated neuron-glioma synapses, ADAM10-NLGN3, BDNF-TrkB;	Treg cell, $CD8^+$ T	• neuronal activity induces glutamatergic synaptic input, activity-dependent NLGN3 release, and adaptive synaptic plasticity, thereby promoting glioma-cell proliferation and network integration	• Preclinical inhibition of AMPAR-, NLGN3-, or TrkB-associated signaling suppresses tumor-associated phenotypes, clinical efficacy remains to be established;
breast cancer brain metastasis	NMDAR-mediated glutamatergic signaling;	T cell	• brain-metastatic cells exploit glutamate released at neuronal synapses and activate NMDAR-dependent calcium signaling to support intracranial survival and outgrowth;	• NMDAR signaling represents a potential target in selected brain-metastatic settings, but clinical validation is lacking;

NGF-TrkA: nerve growth factor-tropomyosin receptor kinase A signaling axis; CGRP-RAMP1: calcitonin gene-related peptide-receptor activity-modifying protein 1 signaling axis; TRPV1: transient receptor potential vanilloid 1; Piezo1: Piezo-type mechanosensitive ion channel component 1; CALCRL: calcitonin receptor-like receptor; M2 macrophage: alternatively activated macrophage; ILC2: group 2 innate lymphoid cell; Treg: regulatory T cell; PAR2: protease-activated receptor 2; HGF: hepatocyte growth factor; c-Met-mTOR: c-Met receptor tyrosine kinase-mechanistic target of rapamycin signaling pathway; TAM: tumor-associated macrophage; MDSC: myeloid-derived suppressor cell; PNI: perineural invasion; TGF-β: transforming growth factor-β; SP-NK1R: substance P-neurokinin 1 receptor signaling axis; A2AR: adenosine A2A receptor; TNF-α: tumor necrosis factor-α; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ADAM10-NLGN3: a disintegrin and metalloproteinase domain-containing protein 10-neuroligin-3 signaling axis; BDNF-TrkB: brain-derived neurotrophic factor-tropomyosin receptor kinase B signaling axis; $CD8^+$ T cell: CD8-positive T cell.

neuroligin-3 (NLGN3) secretion, tumor microtube-mediated electrical coupling, and BDNF- tropomyosin receptor kinase B (TrkB)-associated synaptic plasticity are therefore discussed primarily in the context of glioma. N-methyl-D-aspartate receptor (NMDAR)-dependent pseudo-tripartite interactions are supported mainly by studies of breast cancer brain metastasis. In contrast, neural regulation in extracranial solid tumors is more commonly mediated through autonomic or sensory neurotransmission, neurotrophin-driven nerve recruitment, perineural invasion, and neuroimmune modulation. These distinct levels of evidence should not be considered interchangeable across tumor types.

Tumor-type- and tissue-specific mechanisms of neural-tumor interactions

Tumor progression can be viewed as a dynamic process shaped by tumor-intrinsic programs, neural inputs, and the cellular and molecular composition of the TME, rather than simply restricted to purely intrinsic oncogenic programs and conventional matrix signaling. As presented in Figure 4, tumors are also capable of actively perceiving and integrating multilevel signals from neurons that modulate its biological behavior, such as electrophysiological activity following neurotropic factors, neurotransmitters or ion channels. The mechanisms through which tumor released brain derived neurotrophic factor (BDNF) then goes onto to induce a tumorigenic phenotype are complex, but have been well characterized in gliomas[48,49]. Conversely, the inhibitory neurotransmission is functionally reshaped by tumors, forming autocrine and paracrine networks and inducing immunosuppression that allows immune escape[50]. The effective transmission of these neural signals depends on the structural stability of synaptic adhesion molecules, while ion channels finely regulate the nerve and tumor signaling axis by modulating membrane potential and cellular excitability[51]. The SNS of the peripheral nervous system promotes proliferation, angiogenesis, and metastasis associated pathways through NE[52]. On the other hand, the parasympathetic and sensory nervous systems facilitate tumor development by manipulation of inflammation, vascular permeability or immune cell infiltration[10]. Tumors are able to spread through the low resistance perineural pathway. Hence, the crosstalk between neurons and tumors is not only a common biological characteristic of tumorigenesis but also can be a promising therapeutic target for new ways in constructing therapeutic approaches.

Glutamate-AMPAR signaling in high-grade glioma

Evidence for AMPAR-mediated electrochemical integration is strongest in high-grade glioma. In these tumors, excitatory neuron-to-glioma synapses (NGS) provide a direct route through which neuronal activity can influence malignant cells[53]. Glutamate released from presynaptic neuronal terminals binds to Ca^{2+}-permeable AMPARs expressed on glioma cells, inducing membrane depolarization and intracellular calcium signaling[54,55]. These electrophysiological inputs can be propagated among interconnected glioma cells through connexin 43-associated tumor networks, thereby coordinating calcium activity and proliferative responses[56]. Available evidence is derived predominantly from glioma cell systems, human glioma analyses, and preclinical brain-tumor models. Whether comparable AMPARs-dependent synaptic integration occurs in extracranial solid tumors remains insufficiently established and requires direct electrophysiological and structural validation.

NMDAR-mediated signaling in breast cancer brain metastasis

Evidence for NMDAR-mediated neuron-tumor communication is currently most compelling in models of breast cancer brain metastasis. After colonizing the brain, metastatic breast cancer cells can occupy positions adjacent to pre-existing glutamatergic synapses and form pseudo-tripartite arrangements in which tumor-expressed NMDA receptors sense neuron-derived glutamate[57]. Activation of these receptors promotes calcium influx and downstream signaling that may support metastatic cell survival, adaptation, and outgrowth within the neural microenvironment[58]. NMDAR-dependent effects on migration or viability have also been observed in selected breast cancer cell systems. However, receptor expression or pharmacological responsiveness alone does not demonstrate the formation of functional neuron-tumor synapses outside the brain. Thus, this mechanism should presently be interpreted as a feature of selected brain-metastatic contexts rather than a general mechanism shared by primary breast tumors or other extracranial solid cancers. In this architecture, NMDAR expressed by cancer cells act as microenvironmental sensors. By receiving glutamate signals released between neurons, they trigger persistent calcium influx and downstream CaMKII signaling cascades. This mechanism not only provides crucial survival signals for tumor cells during the process of metastatic colonization but also enables them to exploit the high concentration of excitatory neurotransmitters in the synaptic cleft as a driving force for growth.

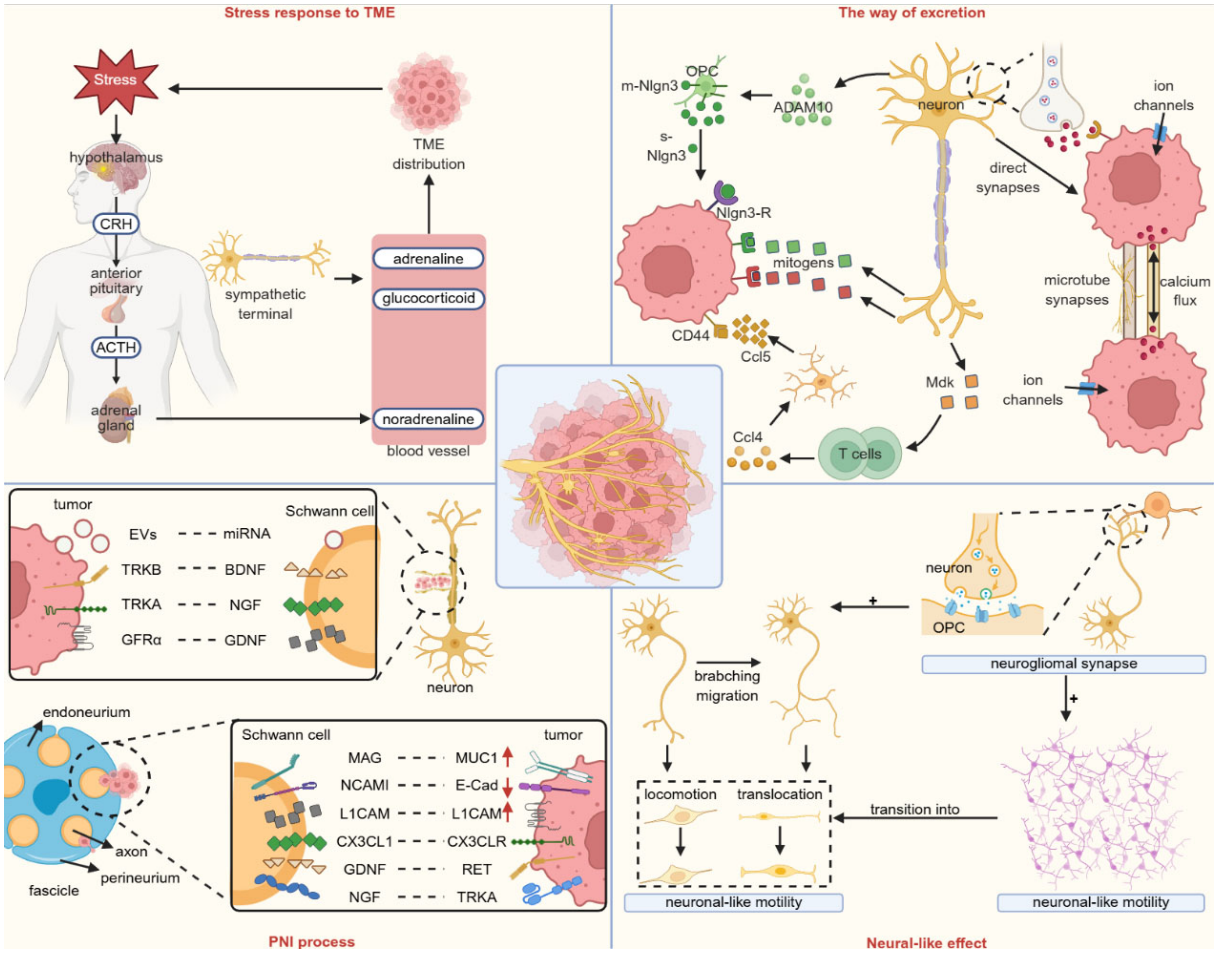

Figure 4. Tumor-type-dependent neural-tumor interactions. Psychological stress activates the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, thereby altering neuroendocrine signaling and the tumor microenvironment across several tumor contexts. Peripheral nerve infiltration, Schwann-cell interactions, neurotrophin signaling, and perineural invasion have been reported in multiple extracranial malignancies. In contrast, AMPAR-mediated neuron-glioma synapses, activity-dependent NLGN3 shedding, NMDAR-dependent pseudo-tripartite interactions, tumor microtube networks, and BDNF-TrkB-associated synaptic plasticity are supported predominantly by studies of glioma and selected brain-metastasis models. These central nervous system-associated mechanisms should not be interpreted as universal features of all solid tumors. TME: Tumor microenvironment; CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone; OPC: oligodendrocyte precursor cell; CD: cluster of differentiation; CCL: C-C motif chemokine ligand; MDK: midkine; ADAM10: a disintegrin and metalloproteinase domain-containing protein 10; NLGN3: neuroligin-3; EV: extracellular vesicle; TrkB: tropomyosin receptor kinase B; TrkA: tropomyosin receptor kinase A; GFRα: glial cell line-derived neurotrophic factor family receptor-α; BDNF: brain-derived neurotrophic factor; NGF: nerve growth factor; GDNF: glial cell line-derived neurotrophic factor; MAG: myelin-associated glycoprotein; NCAM1: neural cell adhesion molecule 1; L1CAM: L1 cell adhesion molecule; CX3CL1: C-X3-C motif chemokine ligand 1; MUC1: mucin 1; CX3CR1: C-X3-C motif chemokine receptor 1; RET: rearranged during transfection receptor tyrosine kinase.

Tumor microtube networks in glioma

The malignant phenotype of gliomas is largely attributable to their unique anatomical architecture: the tumor microtube (TM) network. Driven by GAP43, these elongated tubular protrusions break the individual boundaries between cancer cells[59]. Through connexin 43-mediated gap junctions, they couple scattered tumor cells into a functional multicellular syncytium[60]. Within this architecture, electrical signals from neuronal synapses and glutamate driven calcium influx are no longer confined to local regions[61]. Instead, they are transformed into population wide synchronous calcium oscillations via the TMs network. This networked mode of survival not only endows tumor cells with the ability for coordinated invasion but also constitutes the structural basis for their extreme resistance to radiotherapy and chemotherapy through collective metabolic support and stress buffering. Tumor microtube-mediated multicellular integration has been characterized most extensively in glioma and should not be equated with connexin expression or

intercellular communication observed in other solid tumors. Evidence for structurally and functionally equivalent tumor microtube networks outside the central nervous system remains limited.

Activity-dependent ADAM10-NLGN3 signaling in glioma

Activity-dependent a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10)-NLGN3 signaling has been established primarily in preclinical models of high-grade glioma. Increased neuronal activity promotes ADAM10-dependent ectodomain shedding of membrane-bound neuroligin-3, releasing soluble NLGN3 into the local neural microenvironment[62]. In susceptible glioma cells, soluble NLGN3 activates growth-associated pathways, including phosphatidylinositol 3-kinase (PI3K)-mammalian target of rapamycin (mTOR) and MAPK signaling, and promotes transcriptional programs that support tumor proliferation and neural integration[63]. This interaction may generate a positive feedback loop within the glioma microenvironment by increasing the responsiveness of malignant cells to neural activity. However, NLGN3 should currently be regarded as a context-dependent neural niche factor rather than a universally established mitogen for all solid tumors[64]. Direct evidence for an equivalent activity-dependent ADAM10-NLGN3 circuit in extracranial cancers remains limited.

BDNF-TrkB-associated synaptic plasticity in glioma

The role of BDNF-TrkB signaling in activity-dependent neuron-tumor synaptic plasticity has been characterized mainly in glioma models[65]. Neuron-derived BDNF can activate TrkB expressed by glioma cells and engage downstream PI3K-AKT and MAPK- extracellular regulated protein kinases (ERK) signaling, thereby supporting tumor-cell survival and proliferation[66]. In addition, BDNF-TrkB signaling can enhance the strength and stability of neuron-glioma synaptic interactions, including through changes in postsynaptic AMPA-receptor abundance, thereby establishing an activity-dependent positive feedback loop[67]. Although TrkB expression and BDNF-responsive pro-survival signaling have been reported in several malignancies, the specific role of this pathway in strengthening functional neuron-tumor synapses is currently supported predominantly in the neural microenvironment of glioma. Its applicability to extracranial solid tumors therefore requires independent structural, electrophysiological, and functional validation. These central nervous system-specific synaptic mechanisms should be distinguished from neurotrophin-driven nerve recruitment and perineural invasion, which have broader, although still tumor-dependent, evidence in several extracranial malignancies and are discussed below.

NGF-TrkA pathway

In the remodeling of the TME, the nerve growth factor (NGF)- tropomyosin receptor kinase A (TrkA) pathway serves not merely as a bridge for neural regulation but as a positive feedback amplifier driving malignant progression. Tumor cells actively induce the inward ingrowth of surrounding nerve fibers by secreting NGF to establish a chemotactic gradient, thereby achieving structural reconstruction through neurogenesis[68]. More critically, ingrown neurons and tumor cells form a sophisticated autocrine/paracrine interactive loop via the NGF-TrkA axis. Neuron-derived NGF binds to TrkA receptors on tumor cells, directly driving sustained proliferation and anti-apoptosis through the cascading activation of PI3K/Akt and MAPK/ERK pathways[69]. Simultaneously, the tumor cells' own NGF secretion further maintains the growth promoting state of the microenvironment. This neuro-dependent autocrine loop significantly enhances tumor invasiveness and constitutes the core molecular basis of perineural invasion (PNI)[70]. Therefore, deciphering and blocking this NGF-TrkA feedback axis holds promise as a novel precision therapeutic strategy to inhibit tumor neural invasion and reverse neuro-dependent tumor growth.

Influence the immune system of TME

As shown in Figure 5, within the TME, the nervous system regulates immune cell function by innervating the tumor matrix through nerve fibers and continuously releasing neurotransmitters and neuropeptides. These neural signals influence the migration, spatial distribution, and functional state of immune cells through a chemokine network. Mediators such as sympathetic neurotransmitters, ACh, and calcitonin gene related peptide (CGRP) not only bind directly to receptors on immune cells but also influence immune cell infiltration and migration by modulating the physical and chemical properties of the TME[71-73]. The neurotransmitter NE is also known to modulate T cell migration and effector functions in part by binding to β_2 adrenergic receptors[74]. Acute stress that can act as an immune adjuvant on $CD4^+$ T cell mediated immunity, whereas chronic stress contributes to the failure of remote immune surveillance via induced apoptosis in $CD8^+$ T cells leading to tumor immune escape[75]. In addition, chronic stress and sustained β_2 adrenergic signaling upregulate the production level of ACh that can lead to induced tumor associated macrophages (TAMs) reprogramming into M2 type with immunosuppression effect as well as inhibit TNF production in turn enhance their immune suppressed profile[76,77]. Neuronal signals upregulate immunosuppression and angiogenesis as a consequence of specific receptor scaffolds and downstream pathways, which can favor growth of the neoplasm and spread to distant organs. In addition, nerves control also myeloid derived suppressor cells (MDSCs) and other myeloid populations fueling the tumor immune escape[78]. Therefore, the nerve and tumor axis constitutes a dynamic system in which neurotransmitters, their corresponding receptors, chemokine networks, and the metabolic state of immune cells collectively determine the immune regulatory landscape of the TME, ultimately influencing tumor progression and treatment response.

THE GUT AND TUMOR

The gut microbiota can directly influence tumor cells and the TME through microbial metabolites, structural components, and interactions with intratumoral bacteria. Importantly, these direct interactions do not occur in isolation but coexist with and dynamically integrate with neural signaling pathways, thereby modulating the intensity, spatial distribution, and functional consequences of microbiota driven tumor regulation.

Signaling pathways

Wnt/β-catenin pathway

Dysregulation of the Wnt/β-catenin signaling pathway serves as a central driver in oncogenesis and cancer progression, acting not only as the core engine for epithelial dedifferentiation and malignant transformation but also as a key molecular hub for cross kingdom communication with the gut microbiota. Fusobacterium nucleatum, utilizes its surface adhesin FadA to specifically bind E-cadherin on colonic epithelial cells[79]. This interaction induces endocytosis of the receptor, thereby disrupting the homeostasis of β-catenin anchoring at the cell membrane[80]. Concurrently, the gut microbiota amplifies this signaling cascade by altering the repertoire of local metabolites. Particularly under high fat diet induced bile acid metabolic dysregulation, microbiota derived secondary bile acids act as potent antagonists of the Farnesoid X Receptor (FXR) in the context of compromised genetic stability. Since FXR normally plays a protective role in maintaining intestinal epithelial homeostasis by suppressing β-catenin signaling, this metabolically driven antagonism effectively lifts the negative regulation on the Wnt pathway[81]. It thereby acts as a critical booster in the transformation of colonic stem cells into cancer stem cells. Moreover, this microbe driven signal dysregulation does not exist in isolation. It is intricately intertwined with inflammatory cues in the microenvironment. Microbiota dysbiosis induced chronic inflammation drives the production of abundant pro-inflammatory cytokines via the toll-like receptor 4 (TLR4)/NF-κB axis, leading to STAT3 pathway activation[82]. This pathway not only positively synergizes with Wnt/β-catenin signaling, stabilizing its activated state through epigenetic remodeling, but also collaborates with oncogenic bacteria like Fusobacterium nucleatum to create a conducive niche for tumor growth and immune evasion.

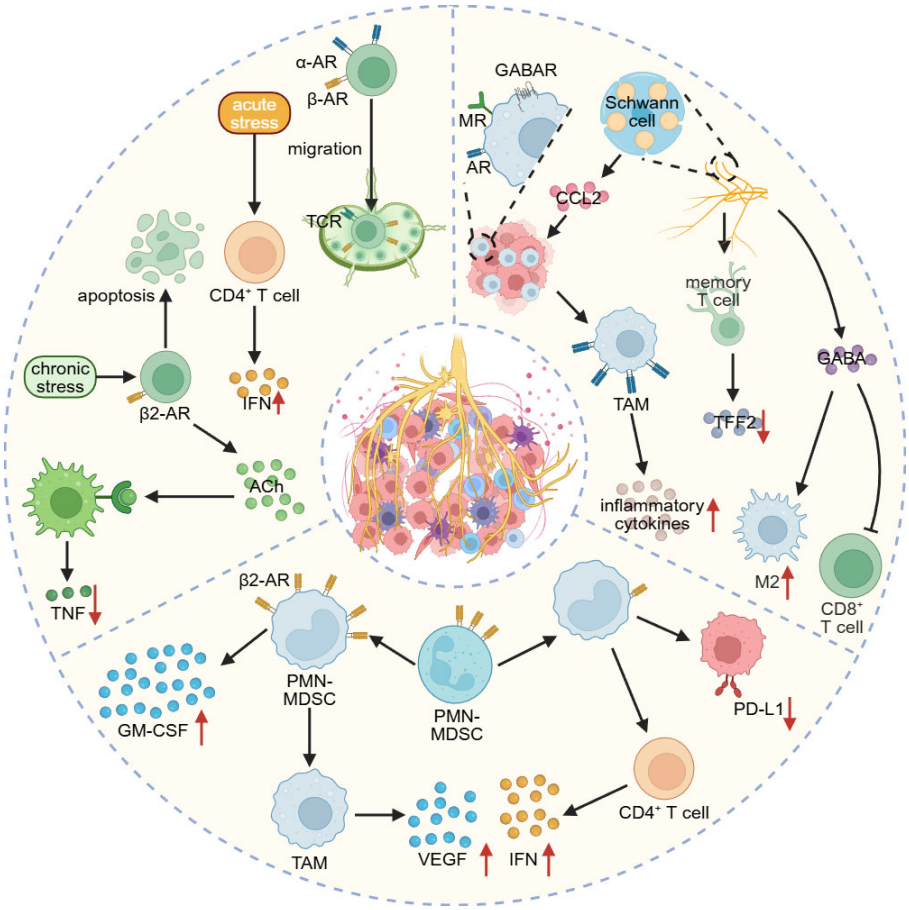

Figure 5. A schematic diagram of neuroimmune interactions within the TME. Sympathetic/parasympathetic nerves and sensory related signals act on T cells, MDSCs, and TAMs via neurotransmitters such as NE and Ach, regulating T cell migration and effector function while driving myeloid-mediated immunosuppression. Acute and chronic stress enhance or inhibit antitumor immunity, respectively. Furthermore, the Schwann cell CCL2 axis promotes TAM recruitment, and T cell derived GABA induces TAM M2 like polarization via GABA receptors, further enhancing immunosuppression. α-AR: α-adrenergic receptor; β-AR: β-adrenergic receptor; TCR: T-cell receptor; CD4⁺ T cell: CD4-positive T cell; GABAR: γ-aminobutyric acid receptor; MR: muscarinic receptor; CCL2: C-C motif chemokine ligand 2; TAM: tumor-associated macrophage; TFF2: trefoil factor 2; TNF: tumor necrosis factor; ACh: acetylcholine; PMN: polymorphonuclear neutrophil; MDSC: myeloid-derived suppressor cell; PD-L1: programmed death-ligand 1; VEGF: vascular endothelial growth factor; IFN: interferon; CD8⁺ T cell: CD8-positive T cell; NE: norepinephrine; GABA: γ-aminobutyric acid.

TLR/NF-κB pathway

During the evolution of the TME, gut derived pathogen associated molecular patterns (PAMPs) function not merely as initiators of local immune responses but as systemic drivers that reshape the immunological landscape of the TME. Dysbiosis of the gut microbiota compromises barrier integrity, allowing bacterial components such as lipopolysaccharide (LPS) and flagellin to translocate across the intestinal epithelial barrier[83]. Upon entering the tumor tissue via systemic circulation, these components bind to pattern recognition receptors (PRRs) on tumor cells and infiltrating immune cells, thereby activating downstream NF-κB and MAPK signaling cascades[84]. Sustained activation of these pathways directly triggers the release of pro-inflammatory cytokines, fostering a chronic inflammatory milieu that promotes cell proliferation and survival. More profoundly, this activation alters the immune tolerance status of the microenvironment through cascade feedback. Specifically, engagement of the LPS/TLR4 axis actively recruits large numbers of MDSCs into the tumor bed by inducing chemokine secretion. Concurrently, this axis, in concert with tumor derived metabolites, drives the polarization of resident macrophages toward an M2 phenotype, significantly enhancing the immunosuppressive functions of these myeloid cells[85]. This microbe driven inflammatory milieu further suppresses anti-tumor immunity through intricate crosstalk mechanisms. In summary, microbe driven PRR activation serves as more than just a signal source for tumor inflammation.

By integrating the recruitment and polarization of myeloid cells, remodeling the cytokine network, and upregulating checkpoint molecules, it constructs a multi layered immunosuppressive barrier. This enables tumors to achieve persistent immune escape and clonal expansion under the surveillance of the host immune system.

STAT3 pathway

In the molecular mechanisms underlying gut microbiota mediated remodeling of the TME, the STAT3 signaling pathway serves not only as a regulatory hub for cell proliferation but also as a critical bridge linking dysbiosis to chronic pro-tumorigenic inflammation. During the pathological progression of colorectal cancer (CRC), sustained activation of STAT3 effectively establishes a permissive condition for tumor growth and immune escape[86]. Enterotoxigenic Bacteroides fragilis (ETBF) is a prototypical pathobiont driving this pathway. The B. fragilis toxin secreted by ETBF acts as the triggering signal, binding to epithelial cell surface receptors and inducing aberrant phosphorylation of STAT3 through a signaling cascade[87]. This cascade, initiated by microbial toxins, integrated by STAT3 signaling, and culminating in immune barrier remodeling, constitutes an indispensable logical circuit in the pro-tumorigenic mechanism of the gut microbiota and tumor axis, greatly accelerating the malignant progression of CRC.

cGAS-STING pathway

As a central sensing mechanism for cytosolic DNA, stimulator of interferon genes (STING) not only serves as a pivotal hub in regulating intrinsic anti-tumor immunity but also enables precision sensitization of immune checkpoint blockade (ICB) therapies through extrinsic microbial intervention. In this context, specific probiotic communities and their metabolites act as potent molecular triggers for pathway activation. Upon local translocation or systemic circulation, these microbial components engage antigen presenting cells and activate the cytosolic sensor cGAS within dendritic cells (DCs), thereby catalyzing the synthesis of cyclic GMP-AMP (cGAMP)[88]. This subsequently propagates the STING-dependent TBK1-IRF3 signaling cascade, prompting robust synthesis and secretion of Type I Interferons (IFN-I)[89]. This axis exerts profound efficacy in reshaping the anti-tumor immune landscape. Ultimately, probiotic driven STING activation creates an optimal responsive niche for immune checkpoint inhibitors (ICIs). By synergistically boosting T cell cytotoxicity and tumor specific responses, this mechanism effectively breaches the tumor's immune escape barriers.

GUT-NEURO-TUMOR SIGNALING FEEDBACK

The gut-neuro-tumor signaling feedback is not intended as a simple combination of the gut-brain axis, gut-tumor axis, cancer neuroscience, and neuroimmune-tumor interactions. Rather, in Figure 6, it integrates these frameworks into a closed-loop sequence consisting of microbial signal generation, neural sensing and processing, coordinated delivery of neuroimmune and metabolic outputs to the TME, and tumor-driven feedback to neural and intestinal homeostasis. This organization enables the nervous system to be considered not merely as a conduit, but as a context-dependent signal-processing layer that can alter the magnitude, timing, and anatomical distribution of microbiota-derived effects. From a therapeutic perspective, this architecture provides multiple interventional entry points at distinct regulatory levels, including modulation of microbial signal sources, recalibration of neural signal integration and amplification, and direct reprogramming of the TME. The evidence supporting this framework can be considered at three levels. Firstly, direct experimental evidence supports individual pairwise relationships, such as microbial metabolites altering neural activity, neural signals modulating tumor or immune cells, and tumors remodeling local nerves or systemic stress responses. Selected studies also indirectly support neural mediation by showing that disruption of vagal, sympathetic, or sensory pathways modifies the biological effects associated with microbial or tumor-derived signals. In addition, the proposition that the

nervous system acts as a dominant integrator and amplifier across the entire gut-neuro-tumor circuit remains hypothetical. No single study has yet traced the complete signal flow across the microbiota, nervous system, TME, and feedback compartments with temporal and causal resolution.

Signaling pathway

Metabo-neural regulatory

Vagus nerve

Within the complex regulatory network of the gut-neuro-tumor signaling feedback, the VN serves as the fastest and most direct bidirectional communication bridge connecting the gut ecosystem to the CNS, playing a pivotal role in signal transduction. This process typically initiates with the precise sensing of microbial metabolites by gut microbiota. Key chemical signals activating vagal afferent fibers include SCFAs, indole and its derivatives, as well as 5-HT secreted by ECs[90]. The most canonical pathway among these is the cholinergic anti-inflammatory pathway. Furthermore, the electrical activity of the VN can remotely modulate the function of tumor infiltrating lymphocytes. In CRC models, enhanced parasympathetic activity reduces the expression of immune checkpoint molecules like PD-1 and PD-L1, consequently boosting the anti-tumor efficacy of $CD8^+$ T cells[91]. However, this regulatory effect exhibits marked organ dependency. In gastric cancer, excessive cholinergic signaling may promote the maintenance of cancer stemness and proliferation by activating the Wnt/β-catenin pathway[92]. This bidirectional loop, initiated by gut microbes, amplified by neural circuits, and ultimately acting upon the tumor immune microenvironment (TIME), not only reveals the precise systemic regulation of local tumors but also provides crucial theoretical support for optimizing cancer therapies through neuromodulation.

Sympathetic nervous system

After receiving and integrating signals derived from the gut microbiota and their metabolites, the central nervous system can regulate the TME through sympathetic neural outputs. Within this bidirectional communication circuit, the sympathetic nervous system is frequently associated with tumor initiation and progression. Norepinephrine released from sympathetic nerve terminals binds to β-adrenergic receptors expressed on tumor cells, stromal cells, and immune cells[93]. Activation of β-adrenergic signaling not only promotes cancer cell proliferation, survival, and migration but also induces an angiogenic switch by upregulating vascular endothelial growth factor and matrix metalloproteinases, thereby facilitating neovascularization within the TIME[94,95]. Furthermore, persistent sympathetic activation induced by chronic psychological stress suppresses the antitumor activity of $CD8^+$ T cells and natural killer cells while enhancing the recruitment and immunosuppressive functions of MDSCs, ultimately promoting tumor immune escape[96].

Parasympathetic nervous system

The parasympathetic nervous system (PSNS) primarily utilizes ACh as its neurotransmitter, yet its impact on tumorigenesis exhibits profound context dependency and organ specificity. In models of gastric and prostate cancer, the infiltration of cholinergic fibers is often positively correlated with pathological progression[92]. In these contexts, ACh binds to muscarinic receptors, subsequently triggering the Wnt/β-catenin or epidermal growth factor receptor (EGFR)/ERK signaling pathways, thereby driving the self-renewal of cancer stem cells and cellular infiltration[97]. However, in breast cancer, PSNS activation demonstrates potential anti-tumor effects[98]. This protective role may be attributed to its ability to downregulate immune checkpoint molecules like PD-1 and PD-L1 via cholinergic signaling, as well as to induce interferon-gamma (IFN-γ) secretion, consequently enhancing local anti-tumor immune responses[99].

Neuro-tumor direct interaction pathway in defined anatomical contexts

Direct neural-tumor interactions include structurally distinct processes whose occurrence varies substantially across tumor types and anatomical sites. Functional electrochemical synapses and activity-dependent neural paracrine signaling have been demonstrated most clearly in primary brain tumors and selected brain-metastatic models[100]. By contrast, direct interactions in extracranial tumors more commonly involve nerve-fiber infiltration, neuropeptide release, neurotrophin signaling, Schwann-cell participation, and perineural invasion[101]. Therefore, the synaptic mechanisms discussed in the following subsections should be interpreted within the specific context of glioma and brain metastasis rather than as universal features of all solid tumors.

Neurogliomal synapse in glioma and brain metastasis

At the terminal end of the gut-neuro-tumor signaling feedback, tumor cells are not merely passive recipients of remote signals but exhibit a high degree of nicotinamide (NAM). The evidence base differs between tumor types. AMPAR-mediated neuron-tumor synapses and connexin 43-associated multicellular networks are best established in high-grade glioma, whereas NMDAR-dependent pseudo-tripartite interactions have mainly been described in breast cancer brain-metastasis models[102,103]. They achieve deep physical and biochemical integration by establishing functional synapses with neurons. The core mechanism underlying this integration lies in the ability of malignant cells, particularly high-grade gliomas and breast cancer brain metastases, to express various neurotransmitter receptors, effectively forming NGS[104]. Metastatic tumors demonstrate a unique synaptic evolutionary strategy, and they form structures known as pseudo tripartite synapses by expressing NMDARs. In this configuration, tumor cells occupy the niche typically held by astrocytes in physiological conditions[105]. By continuously scavenging glutamate released from neurons, they activate their own NMDAR pathways, thereby gaining a survival advantage and accelerating colonization and expansion within the challenging brain microenvironment[103]. Notably, the impact of synaptic input is not isolated to single cells. Instead, it is amplified through tumor networks physically coupled by gap junctions, connexin 43. This synchronized calcium wave propagation allows the entire tumor syncytium to respond to neural signals in concert, forming a multicellular integrated network akin to a brain within the brain[106]. This significantly enhances the tumor's tolerance to stress injuries. Furthermore, tumors hijack adaptive plasticity mechanisms from the nervous system, such as the BDNF-TrkB pathway, to strengthen synaptic connectivity and quantity, establishing a positive feedback loop that fuels malignant evolution[67]. These studies establish a mechanistic basis for neural activity-dependent progression in glioma and selected brain metastases. However, comparable functional synaptic integration has not been demonstrated consistently in extracranial primary tumors, and its prognostic or therapeutic relevance should therefore be evaluated separately for each tumor type and anatomical context.

Activity-dependent neural paracrine signaling in glioma

Within the remote regulation and terminal effects of the gut-neuro-tumor signaling feedback, paracrine factors secreted by neurons constitute a pivotal biochemical signaling network that reshapes the TME. This regulatory mechanism not only provides direct pro-growth stimuli to tumor cells but also induces highly malignant evolutionary traits by mimicking neurodevelopmental pathways. NLGN3 is currently one of the most extensively studied neuroactivity dependent oncometabolites. In the tumor context, neuronal electrical activity induces the upregulation of the protease ADAM10, which precisely cleaves membrane bound NLGN3, facilitating its shedding into secreted neuroligin-3 (sNLGN3) released into the microenvironment[107]. Once secreted, sNLGN3 binds to receptors on tumor cells, significantly accelerating the proliferation and infiltration of malignancies such as gliomas by potently activating canonical oncogenic pathways including PI3K-mTOR, and ERK[108]. Of particular importance, this interaction often evolves into a vicious feedback loop. The PI3K pathway activated within tumors can further induce tumor cells themselves to express NLGN3, thereby continuously reinforcing their survival advantage through an

autocrine mode[109]. In glioma, BDNF-TrkB signaling contributes to activity-dependent synaptic plasticity and may strengthen the functional integration of malignant cells with surrounding neural circuits. This synaptic role should be distinguished from the broader prosurvival effects of BDNF-TrkB signaling reported in other cancer-cell systems[110]. This mechanism essentially represents tumor cells hijacking the brain's learning and memory plasticity machinery. By strengthening electrophysiological connections with neural circuits, tumors secure sustained nutritional support and immune evasion capabilities. Furthermore, insulin-like growth factor-1 reveals the initiating mechanisms by which external environmental stimuli drive tumorigenesis through neuro paracrine signaling[111]. Notably, microbial metabolites produced via the gut-brain axis have been shown to modulate central levels of factors like BDNF[112]. This suggests that distal signals from the gut may indirectly determine the susceptibility and progression rate of central nervous system tumors by regulating the abundance of neural paracrine factors.

Neuro-immune-tumor pathway

The influence of the nervous system on tumor progression transcends direct physical contact or chemical stimulation, extending profoundly into the systemic remodeling and precise modulation of the TIME.

Remodeling of the TIME

Within the framework of the gut-neuro-tumor signaling feedback, the systemic remodeling of the immunosuppressive environment is not merely a byproduct of neuroactivity, but rather a core mechanism by which the nervous system precisely modulates the TIME. Specifically, the SNS plays a major driving role in this remodeling process. NE released from SNS nerve terminals binds to β_2-adrenergic receptor (β_2-AR) on immune cells[51]. This interaction activates the cyclic adenosine monophosphate (cAMP)- protein kinase A (PKA) signaling pathway, thereby significantly inducing the recruitment and functional enhancement of MDSCs, as well as driving the polarization of TAMs toward a pro-tumoral M2 phenotype[113]. Furthermore, neuropeptides secreted by sensory neurons play an indispensable role in shaping this immunosuppressive landscape. This neuro immune interplay is ultimately unified within the macro-context of the gut-brain axis. Gut microbiota and their metabolites, by regulating systemic immune homeostasis, can induce the differentiation of forkhead box P3 (Foxp3+) Tregs, thereby supporting or suppressing local immune remodeling at a systemic level[114]. Concurrently, upon receiving gut derived signals, the CNS releases glucocorticoids via the hypothalamic-pituitary-adrenal (HPA) axis[115]. These hormones further synergize with sympathetic signals to suppress both innate and adaptive immune responses[116]. Therefore, the neural remodeling of the immunosuppressive milieu is a multi-tiered process. It weaves together the biochemical signals from gut microbiota, the electrophysiological signals from peripheral nerves, and the reconstructed local immune boundaries.

Parasympathetic/vagal immune regulation

Within the regulatory framework of the gut-neuro-tumor signaling feedback, the parasympathetic nervous system plays a pivotal inhibitory role in maintaining immune homeostasis within the TME via neuro-immune reflex circuits. ACh, the primary neurotransmitter released by vagal efferent fibers, binds to alpha-subunit of acetylcholine receptor (α-AChR) on the surface of myeloid immune cells[117]. This interaction activates the cholinergic anti-inflammatory pathway, significantly suppressing the production and release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1β, interleukin-6 (IL-6), and IL-18[118]. This top and down immunomodulatory mechanism not only alleviates the chronic inflammatory milieu that drives tumor progression but also reshapes the immune cell landscape within the TME. In pancreatic cancer, cholinergic signaling exhibits significant anti-tumor activity by reducing the pro-tumoral polarization of TAMs and diminishing cancer stem cell phenotypes[119]. However, the contribution of vagal signaling to host immune defense is most intuitively demonstrated in ablation studies. In pancreatic ductal adenocarcinoma (PDAC) models, surgical vagotomy leads directly to increase $CD8^+$ T

cell infiltration, an imbalance in helper T cell ratios, and aberrant activation of macrophage-mediated inflammatory signaling pathways[120,121]. This systemic impairment of immune surveillance not only lifts the suppression on tumor growth but also accelerates early lesion onset and migration, ultimately significantly shortening survival. This negative feedback mechanism within the neuro-immune-tumor axis reveals that metabolites produced by gut microbiota may trigger central responses via vagal afferent fibers, which then achieve remote fine-tuning of the local tumor immune landscape via vagal efferent fibers and cholinergic pathways. It is worth noting that this immunomodulatory role of the vagus nerve is highly tissue-specific. Although it manifests as an anti-tumor effect in pancreatic cancer, cholinergic signaling may conversely promote tumor cell proliferation by activating the M3R/Wnt signaling pathway in gastric cancer[122].

Tumor-mediated regulation of the gut and nervous system

Within the gut-neuro-tumor signaling feedback, tumors are not merely passive recipients of microbial and neural signals. Instead, they actively reshape this cross-system network through two complementary mechanisms. Locally, tumors promote neoneurogenesis and PNI by recruiting and remodeling peripheral nerves. Systemically, tumors disturb brain activity, activate the HPA axis, and impair intestinal and microbial homeostasis. Together, these local and systemic feedback routes reinforce tumor progression, immune dysregulation, and therapeutic resistance.

Neoneurogenesis and perineural invasion

Within the dynamic interplay of the gut-neuro-tumor signaling feedback, tumors are not merely passive recipients of signals. Instead, they actively reshape the local microenvironment and accelerate their malignant progression by inducing neoneurogenesis and PNI. This process often begins with the tumor's targeted recruitment of the nervous system. Through paracrine signaling, tumor cells secrete a variety of neurotrophic factors, including NGF, BDNF, and glial cell line-derived neurotrophic factor (GDNF)[123]. Analogous to angiogenic factors, these molecules induce the sprouting of new axons into the tumor mass, resulting in a significant increase in intratumoral nerve fiber density, often several fold higher than in non-tumorous tissues[124]. This active recruitment of nerve fibers provides tumor cells with a unique migratory pathway. During PNI, malignant cells migrate and spread along the nerve sheaths, frequently exhibiting neural tracking behavior[125]. Notably, this process can occur even prior to lymphatic or vascular involvement. Such invasion relies not only on physical contact but also involves the formation of a specialized perineural niche. Within this unique biochemical microenvironment, invading tumor cells disrupt the perineurium, triggering a cascade of inflammatory cytokines that further promote both neural remodeling and tumor cell survival[126,127]. Collectively, neoneurogenesis and perineural invasion establish a local positive feedback loop in which tumors recruit and remodel neural structures, while the resulting neural inputs further support tumor survival, invasion, and immune evasion. Beyond this local neural remodeling, tumors can also perturb central neuroendocrine regulation and intestinal homeostasis, as discussed in the following subsection.

Tumor-induced disruption

Tumors do not merely respond to neural signals but can actively disrupt central nervous system function and its homeostatic communication with the gut. At the local level, glioma cells release excessive amounts of excitatory neurotransmitters, particularly glutamate, resulting in markedly elevated extracellular glutamate concentrations in the peritumoral region and increased excitability of surrounding neurons[128]. This neuronal hyperexcitability constitutes an important mechanism underlying tumor-associated epilepsy. At the systemic level, cancer and cancer-associated psychological or physiological stress can chronically activate the hypothalamic-pituitary-adrenal axis, increasing the release of glucocorticoids and catecholamines[129,130]. Persistent HPA-axis activation subsequently alters gastrointestinal motility, mucosal secretion, immune regulation, and epithelial barrier integrity through descending neuroendocrine and

autonomic pathways[131]. These changes can disrupt gut microbial homeostasis, typically reducing the abundance of short-chain fatty acid-producing bacteria while favoring the expansion of potentially pathogenic taxa[132]. Barrier impairment may further facilitate the entry of microbial products and inflammatory mediators into the systemic circulation. These circulating signals can aggravate neuroinflammation and reshape the tumor immune microenvironment, thereby feeding back to support tumor progression and immune escape[133]. Consequently, a tumor-initiated process can be amplified through central neuroendocrine signaling and gut dyshomeostasis before returning to the TME. This forms a self-reinforcing systemic feedback loop that extends the biological effects of a localized tumor beyond its primary anatomical site.

Gut-tumor microbiota

The gut-tumor microbiota axis constitutes the cutting edge of research into the TME, revealing profound spatial coupling and functional synergy between the intestinal ecosystem and spatially segregated neoplastic tissues. At the core of this axis lies the mechanism by which gut microbiota, serving as a primary reservoir, undergo translocation and establish colonization within tumor sites through diverse biological pathways.

Intratumoral bacteria

In Table 3, within the dynamic interplay of the gut-neuro-tumor signaling feedback, microbial translocation is not merely the material basis for biochemical signal transduction but also the spatial prerequisite for the evolution of gut commensals into intratumoral microbiota. The gut, serving as the body's largest microbial reservoir, allows its microbiota to cross anatomical boundaries under pathological conditions. These microbes migrate to distal tumor sites via barrier injury, systemic circulation, and anatomical retrograde pathways[134]. This spatial relocation of microbes ultimately establishes a distinct colonization pattern within the tumor locale. The TME, characterized by hypoxia, nutrient enrichment, and immunosuppression, provides an ideal niche for these translocated microbes[135]. They are able to persist in an intracellular manner, residing within the cytoplasm of either tumor cells or immune cells. These colonized intratumoral bacteria are not passive bystanders. By producing metabolites, inducing host DNA damage, and activating oncogenic pathways, they actively participate in shaping the TME[136].

Direct mechanisms

Some microbial products directly induce genomic instability or activate oncogenic signaling, whereas others modulate antitumor immunity, epithelial barrier integrity, or treatment responsiveness[137]. Beyond such direct genotoxic injury, microbes drive the evolution of the malignant phenotype by precisely hijacking the host's pre-existing signaling networks[138]. In this regard, the aberrant activation of the Wnt/β-catenin pathway is considered a key pathological mechanism[139]. This multidimensional mechanism, ranging from physical damage to the systematic subversion of oncogenic signaling, transforms microbes from mere biological bystanders into co-drivers of tumor initiation and progression. As summarized in Table 4, microbiota-derived metabolites, structural components, virulence factors, and other bioactive products can exert either tumor-promoting or tumor-suppressive effects. These effects are highly dependent on the chemical identity of the microbial product, its concentration, the host and tumor context, and the experimental model. They thus constitute a critical cornerstone of biochemical communication within the gut-neuro-tumor signaling feedback.

Tissue-specific organization and applicability

The relative contribution of each component of the gut-neuro-tumor signaling feedback varies substantially across tumor types and anatomical sites. No individual neural, microbial, or immune mechanism should therefore be regarded as universally active in all cancers. Instead, the framework contains broadly recurrent

Table 3. Common tumor types and the role of intratumoral bacteria

Cancer	Microbiota	Effect in tumor
Colorectal cancer	*Fusobacterium nucleatum*, *Bacteroides fragilis*, *Peptostreptococcus anaerobius*, *Providencia*, *Firmicutes*, *Bifidobacterium pseudolongum*, *Parvimonas micra*, *Prevotella*, *etc.*	• Produces colibactin and CagA, disrupting WNT, ATM signaling pathways of host cell, and promotes tumor progression: interacts with the TME to enhance tumor growth;
Gastric cancer	*Helicobacter pylori*, *Lactobacillus*, *Prevotella*, *Bacteroidetes*, Proteobacteria, *etc.*	• *H. pylori* infection is a major risk factor for gastric cancer and triggers chronic inflammation through virulence factors such as CagA, promoting gastric cancer development;
Breast cancer	*Staphylococcus epidermidis*, *Streptococcus agalactiae*, *Lactobacillus*, *Corynebacterium*, *Fusobacterium nucleatum*, *Butyricimonas*, *Sphingomonas*, *etc.*	• *Bacillus*, *Enterobacteriaceae*, and *Staphylococcus* possess DNA-damaging capabilities, Beneficial bacteria such as Lactobacillus exhibit anti-cancer properties and Lactobacillus promotes an immunosuppressive microenvironment, influencing tumor progression;
Lung cancer	*Brevundimonas*, *Pseudomonas*, *Acinetobacter*, *Streptococcus*, *Corynebacterium*, *Lachnoanaerobaculum*, *Halomonas*, *etc.*	• Promotes chronic inflammation through IL-6/STAT3 pathway and modulates tumor-associated macrophages;
Pancreatic ductal adenocarcinoma	*Gammaproteobacteria*, Malassezia spp, *Fusobacterium nucleatum*, *Granulicatella adiacens*, *Acidovorax ebreus*, *Acinetobacter baumannii*, *Geobacillus kaustophilus*, *Escherichia coli*, *Granulicatella adiacens*, *Acinetobacter*, *Pseudomonas*, *Sphingopyxis*, *etc.*	mediates gemcitabine inactivation through bacterial cytidine deaminase and promotes immune suppression via TLR and Dectin-1 signaling;
Prostate cancer	*Propionibacterium acnes*, *Escherichia coli*, *Escherichia*, *Propionibacterium*, *Acinetobacter*, *Pseudomonas*, *etc.*	induces chronic prostatitis and DNA damage, activates IL-6/STAT3 pathway contributing to tumor growth;

CagA: cytotoxin-associated gene A protein; WNT: Wingless-related integration site signaling pathway; ATM: ataxia telangiectasia mutated kinase; TME: tumor microenvironment; IL-6: interleukin-6; STAT3: signal transducer and activator of transcription 3; TLR: Toll-like receptor.

regulatory modules whose activity, direction, and magnitude are determined by tissue-specific innervation, neurotransmitter-receptor expression, microbial composition, stromal architecture, vascular and barrier properties, and the local immune context. Some mechanisms are strongly restricted by anatomical context. Functional electrochemical coupling through AMPAR-mediated neuron-glioma synapses, activity-dependent ADAM10-NLGN3 signaling, tumor microtube networks, and BDNF-TrkB-associated synaptic plasticity has been demonstrated predominantly in glioma[110]. NMDAR-dependent pseudo-tripartite interactions are supported mainly in breast cancer brain-metastasis models[103]. These mechanisms depend on the specialized neural microenvironment of the central nervous system and cannot currently be extrapolated to extracranial tumors. By contrast, autonomic and sensory neurotransmission, neurotrophin-mediated nerve recruitment, perineural invasion, and neuroimmune regulation have been reported across several extracranial malignancies, although their functional consequences remain organ dependent[198]. Cholinergic signaling, for example, may promote cancer stemness and proliferation in gastric and prostate cancer models, whereas parasympathetic or vagal activity has shown antitumor effects in selected breast and pancreatic cancer models[199,200]. Similarly, sympathetic and sensory signals may act through different receptor populations and immune-cell compositions in different TME. Microbial regulation is also tissue specific. Gastrointestinal tumors are directly exposed to local microbial communities and microbial products, whereas distant tumors may be influenced predominantly through circulating metabolites, systemic immunity, microbial translocation, or treatment-associated changes in gut microbiota. Intratumoral microbial composition also differs among colorectal, gastric, pancreatic, breast, lung, and prostate cancers, resulting in distinct effects on inflammation, metabolism, immune suppression, and therapeutic response. Accordingly, the most broadly shared feature of the proposed framework is not a single molecular pathway but the organizational principle that microbial, neural, immune, and tumor-derived signals can interact bidirectionally. The specific molecular modules involved must be defined separately for each tumor type, disease stage, anatomical site, and experimental model.

Table 4. Representative microbiota-derived metabolites, microbial structural components, virulence factors, and bioactive products affecting tumor biology

Class of microbial product	Metabolites	Microorganisms	Functions	Refs
Amino acid derivative	Taurine	Deltaproteobacteria;	• Regulates the activity of NLRP6 in intestinal epithelial cells and maintaining intestinal microbial homeostasis and ameliorating colitis;	[140]
	Hippurate	increased in association with a *Bifidobacterium*-enriched microbiota;	• Enhances NK-cell-dependent antitumor immunity in a high-salt diet mouse model under IFN-γ-associated conditions;	[141]
	GABA	*Bacteroides*, *Lactobacillus*, *Bifidobacterium*, *Parabacterium*;	• Regulates the ability of multiple immune cells to kill tumors by modulating gut-brain axis;	[142, 143]
	S-adenosylmethionine	*Saccharomyces cerevisiae*, *Pichia pastoris*, *Candida utilis*, *Escherichia coli*;	• S-adenosylmethionine participates in tumor and immune-cell methyl-donor metabolism, and its effects are tumor- and dose-dependent, with available studies reporting modulation of $CD8^+$ T-cell function and antiproliferative effects in selected prostate and liver cancer models;	[144-147]
Tryptophan	Kynurenic acid	*Lachnospiraceae*, *Enterococcaceae*;	• Blocks the proliferation of colon cancer cells by inhibiting MAPK and PI3K-Akt signaling pathways, provides long-term radioprotection and reduces proinflammatory responses;	[148-150]
	histamine	*Klebsiella aerogenes*;	• Disrupts the NLRP6-IL-18-AMP axis and thus exacerbating colitis;	[140]
	indole	*Escherichia coli*, *Bacteroides thetaiotaomicron*, *Bacteroides ovatus*, *C. limosum*;	• Suppress inflammation, fix abdominal wall structures, AhR ligands;	[151-153]
	IAA	*Bacteroides ovatus*, *Bacteroides fragilis*, *Escherichia coli*;	• Suppress inflammation, fix abdominal wall structures, AhR ligands;	[154-158]
	TMAO	*Enterobacteriaceae*, *Clostridiales*;	• Promotes the proliferation of HCT116 cells;	[159, 160]
	3-IAld	*Lactobacillus reuteri*;	• Provides long-term radioprotection and prevents intestinal damage triggered by ICB therapy, enhances the effect of immunotherapy for pancreatic cancer and triple-negative breast cancer;	[161, 162]
	IPA	*Clostridium sporogenes*;	• Promotes the development of non-alcoholic fatty liver disease-associated hepatocellular carcinoma;	
Virulence factors	FadA	*Fusobacterium nucleatum*;	• Mediates adhesion and invasion of epithelial and endothelial cells;	[163-165]
	Fap2	*Fusobacterium nucleatum*;	• Immunity, binds to Gal-GalNAc;	[166-168]
	LPS	*Gram-negative bacteria*;	• promotes cancer progression by activating TLR4 signaling that induces inflammation;	[169, 170]
	MDP, GMDP	*Enterococcus faecalis*;	• Activate immune system by binding to NOD2 on the surface of immune cells and activating NF-κB signaling	[171, 172]

BAs	DCA	*Clostridium hiranonis*, *Clostridium hylemonae*, *Clostridium sordellii*, *Clostridium scindens*, *Bacteroides*;	• Promotes EMT and the formation of vasculogenic mimicry in cancer;	[173, 174]
	LCA	*Bacteroides*, Eubacterium, Escherichia, *Lactobacillus*, *Clostridium hiranonis*, *Clostridium hylemonae*, *Clostridium sordellii*, *Clostridium scindens*;	• In colorectal cancer cells, LCA can induce IL-8 and miR-21-associated PTEN suppression through ERK/STAT3-related signaling; • In selected breast cancer and nephroblastoma cell models, LCA has been reported to inhibit lipogenesis or induce apoptosis;	[174-178]
	UDCA	*Clostridium*, *Parabacteroides distasonis*;	• Prevents colon cancer progression by inhibiting NF-κB signaling and suppressing the upregulation of Cox-2;	[179, 180]
SCFAs	Acetate	Bacteroides. Hydrogenotrophica, *M ethanobrevibacter smithii*, *Ruminococcus gnavus*;	• Suppress the proliferation and induce apoptosis of tumor, especially the colon cancer, mainly through activating G-protein coupled receptors and inhibiting histone deacetylases, AhR signaling, cancer stemness, inflammation; • Butyrate supports intestinal barrier integrity through HIF-dependent mechanisms and can suppress colonic inflammation and its direct antitumor effects depend on tumor genotype, concentration, and metabolic context;	[181-183]
	Butyrate	Roseburia intestinalis, Butyrivibriocrossotus, *Faecalibacterium cf. prausnitzii*;		[184, 185]
Aldehydes	Reuterin	*Lactobacillus reuteri*;	• Restricts colon tumor growth by inducing oxidative stress and inhibiting protein translation;	[186]
Purine nucleoside	Inosine	*Bifidobacterium pseudolongum*;	• Inhibits UBA6 to augment the immunogenicity of tumors and promotes Th1 differentiation in the existence of exogenous IFN-γ;	[187, 188]
Tryptophan metabolite	Kynurenic acid	*Lachnospiraceae*, *Enterococcaceae*;	• Blocks the proliferation of colon cancer by inhibiting MAPK and PI3K-Akt signaling pathways, provides long-term radioprotection and reduces proinflammatory responses;	[189]
Antibiotic	Manumycin A	*Streptomyces sp.*;	• Prevents cancer progression by inhibiting Ras farnesylation and the biosynthesis and secretion of exosomes;	[190-192]
Ellagitannin-derived phenolic metabolite	Urolithin A	*Enterococcus faecium* FUA027 converts ellagic acid into UA	• UA suppresses PI3K/AKT/mTOR signaling and inhibits pancreatic cancer growth;	[193, 194]
daidzein	S-equol	*Lactococcus garvieae*;	• Prevents the proliferation of human breast cancer MCF-7 cells by up-regulating miR-10a-5p;	[195]
Microbiota-derived gallic acid	Specific producer not assigned unless directly demonstrated	In defined intestinal contexts, gallic acid can convert particular mutant p53 proteins from tumor-suppressive to oncogenic activity;	• Promotes cancer progression by switching mutant p53 from tumor-suppressive to oncogenic;	[196]
Vitamin	niacin	*Lactobacillus*, *Bacteroides xylanisolvens*;	• Possesses both pro- and anti-cancer effects that depend on the concentration of niacin;	[197]

NLRP6: NOD-like receptor family pyrin domain-containing 6; NK: natural killer cell; IFN-γ: interferon-γ; GABA: γ-aminobutyric acid; MAPK: mitogen-activated protein kinase; PI3K: phosphoinositide 3-kinase; AKT: protein kinase B; $CD8^+$ T cell: CD8-positive T cell; AhR: aryl hydrocarbon receptor; IAA: indole-3-acetic acid; TMAO: trimethylamine N-oxide; 3-IAld: indole-3-aldehyde; IPA: indole-3-propionic acid; ICB: immune checkpoint blockade; FadA: Fusobacterium adhesin A; Fap2: Fusobacterium autotransporter protein 2; Gal-GalNAc: galactose-N-acetylgalactosamine; LPS: lipopolysaccharide; MDP: muramyl dipeptide; GMDP: glucosaminyl muramyl dipeptide; NOD2: nucleotide-binding oligomerization domain-containing protein 2; NF-κB: nuclear factor-κB; TLR4: Toll-like receptor 4; BAs: bile acids; DCA: deoxycholic acid; LCA: lithocholic acid; IL-8: interleukin-8; miR-21: microRNA-21; PTEN: phosphatase and tensin homolog; ERK: extracellular signal-regulated kinase; STAT3: signal transducer and activator of transcription 3; UDCA: ursodeoxycholic acid; COX-2: cyclooxygenase-2; SCFAs: short-chain fatty acids; HIF: hypoxia-inducible factor; UBA6: ubiquitin-like modifier-activating enzyme 6; Th1: T helper 1 cell; Ras: rat sarcoma virus GTPase; UA: urolithin A; mTOR: mechanistic target of rapamycin; MCF-7: Michigan Cancer Foundation-7 human breast cancer cell line; miR-10a-5p: microRNA-10a-5p; p53: tumor protein p53.

INVESTIGATIONAL THERAPEUTIC STRATEGIES AND CLINICAL TRANSLATION

Targeting the gut-neuro-tumor signaling network represents an emerging area of translational oncology. The interventions summarized in Table 5 include repurposed neurological or cardiovascular drugs, microbiota-based interventions, live biotherapeutic candidates, microbial vaccines, and antibiotic-based strategies. However, these approaches differ substantially in their stage of development, study objectives, and strength of clinical evidence. Most available data are derived from preclinical studies, observational analyses, phase 0 or phase I studies, small early-phase trials, or exploratory biomarker studies rather than confirmatory randomized clinical trials. Importantly, none of the β-blocker, bethanechol, botulinum toxin, fecal microbiota transplantation, or probiotic/live biotherapeutic strategies listed in Table 5 is currently approved as an antineoplastic treatment for malignant tumors. Some individual agents have established regulatory approval for non-oncological indications. Similarly, approved fecal microbiota products are indicated for the prevention of recurrent Clostridioides difficile infection and not for cancer treatment. Their use in oncology should therefore be regarded as investigational, repurposed, or adjunctive rather than as established standard-of-care therapy. Early clinical studies nevertheless provide a rationale for continued investigation. Microbiota-directed approaches such as fecal microbiota transplantation (FMT) and selected live biotherapeutic products have been evaluated as potential modifiers of immune-checkpoint inhibitor responsiveness, whereas β-adrenergic blockade and cholinergic modulation have been explored as methods of altering neural and immune signaling within the TME. These findings remain preliminary and should not be interpreted as proof of clinical benefit. Further development requires adequately powered randomized trials, tumor-specific efficacy endpoints, biomarker-guided patient selection, standardized product manufacturing, and systematic evaluation of infection, cardiovascular, autonomic, and immune-related safety risks. Collectively, these studies support the biological plausibility of targeting neural and microbiota-related components of the tumor ecosystem, but they do not yet establish a new standard of cancer care. Registered trials, preliminary response signals, or biomarker changes should not be equated with confirmed improvements in survival or durable tumor control. At present, these interventions should generally be used in oncology only within appropriately designed clinical studies. Future translation will require randomized and adequately powered trials, predefined tumor-specific clinical endpoints, validated predictive biomarkers, standardized intervention protocols, and long-term safety assessment.

CONCLUSION AND PROSPECTS

Conclusion

Conceptually, the gut-neuro-tumor signaling feedback should not be viewed as a linear signaling cascade, but rather as a dynamic control system composed of distributed regulatory nodes spanning the microbiota, neural circuits, and the TME. Within this conceptual framework, the nervous system is proposed to function as a context-dependent intermediary that may integrate, filter, and spatially redistribute selected microbial and immune signals. Although the individual microbiota-neural, neural-tumor, and tumor-host interactions are supported by experimental evidence, their organization into a unified hierarchical cascade remains to be directly validated. The gut microbiome directly or indirectly impacts neural activity and neurotransmitter balance through the production of metabolites like SCFAs, bile acids, and tryptophan derivatives. These microbial metabolites also affect immune cell function and stromal TME states. Conversely, the nervous system can also adjust gut microbiota configuration via autonomic and neuropeptide signaling forming a bidirectional regulatory loop. Tumors, however, are not passive. They modulate this axis by releasing inflammatory mediators, facilitating dysbiosis and for increased neural remodeling, in turn impacting the tumorigenic milieu with enhanced immunosuppression, metabolic alterations and treatment resistance. This framework provides a mechanistic explanation for the context dependent and often paradoxical effects of microbial metabolites, neurotransmitters, and stress-related factors in cancer, and highlights why targeting a single molecular pathway frequently yields limited

Table 5. Selected registered clinical studies evaluating investigational neural- and microbiota-targeted strategies in oncology

Cancer type	Combined drugs	Trials No.	Trial phase	Trial status
Nervous system				
prostate cancer	carvedilol	NCT02944201	phase 2	unknown status
hepatocellular carcinoma	propranolol and carvedilol	NCT06233708	NA	completed
malignant soft tissue sarcoma	propranolol and doxorubicin	NCT03108300	phase 2	unknown status
pancreatic; hepatocellular; biliary tract cancer	propranolol, ICIs, and paclitaxel	NCT05451043	phase 2	recruiting
PDAC	propranolol	NCT06145074	phase 2	recruiting
breast cancer	carvedilol	NCT02177175	phase 2	completed
breast cancer	carvedilol	NCT01724450	phase 3	completed
breast cancer; melanoma	propranolol	NCT02013492	early phase 1	completed
prostate cancer	propranolol	NCT03152786	phase 2	terminated
advanced melanoma	propranolol, naltrexone, and ICIs	NCT05968690	phase 1	recruiting
cancer bone metastases	tanezumab	NCT02609828	phase 3	completed
PDAC	bethanechol	NCT03572283	early phase 1	completed
prostate cancer	botulinum toxin	NCT01520441	early phase 1	withdrawn
FMT				
GIT cancers	FMT with anti-PD-1	NCT04130763	phase 1	completed
metastatic mesothelioma	FMT with anti-PD-1 and pembrolizumab therapy	NCT04056026	early phase 1	completed
advanced melanoma	FMT with anti-PD-1	NCT03353402	phase 1	unknown status
advanced melanoma	FMT with anti-PD-1 and pembrolizumab therapy	NCT03341143	phase 2	active, not recruiting
advanced melanoma	FMT with anti-PD-1 and pembrolizumab/nivolumab therapy	NCT03772899	phase 1	active, not recruiting
RCC	FMT with anti-CTLA-4, anti-PD-1 and immune-related colitis of ipilimumab/nivolumab therapy	NCT04163289	phase 1	active, not recruiting
Probiotics and investigational live biotherapeutic products				
advanced RCC	Clostridium butyricum CBM 588 with anti-PD-1 and anti-CTLA-4	NCT03829111	phase 1	completed
advanced solid tumors	MRx0518(Enterococcus gallinarum), with anti-PD-1 and pembrolizumab treatment	NCT03637803	phase 1	terminated
metastatic melanoma	SER-401 with anti-PD-1, antibiotic(vancomycin) and nivolumab treatment	NCT03817125	phase 1b	NA
solid tumors	MET-4 in combination with ICBs;	NCT03686202	phase 2/phase 3	active, not recruiting
advanced melanoma	EDP1503(Bifidobacterium spp.) with anti-PD-1 and pembrolizumab;	NCT03595683	phase 2	NA
Vaccines				
nonmuscle-invasive bladdercancer	Ty21a (typhoid)	NCT03421236	phase 1	completed
metastatic castration-resistant prostatecancer	JNJ-64041809 (live attenuated double-deleted Listeria monocytogenes)	NCT02625857	phase 1	completed
CRC with liver metastasis	VXM01(live attenuated Salmonella typhimurium carryingVEGFR2)	NCT02718430	phase 1	completed
Antibiotics				
pancreatic adenocarcinoma	Antibiotics (ciprofloxacinand metronidazole) with pembrolizumab	NCT03891979	phase 4	withdrawn
Advanced cancer	Antibiotics (antibacterial, antifungal, antiprotozoal agents)	NCT02366884	phase 2	unknown status

NCT: ClinicalTrials.gov identifier; NA: not available; PDAC: pancreatic ductal adenocarcinoma; ICI: immune checkpoint inhibitor; FMT: fecal

microbiota transplantation; GIT: gastrointestinal tract; PD-1: programmed cell death protein 1; RCC: renal cell carcinoma; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; CBM588: Clostridium butyricum MIYAIRI 588; MRx0518: Enterococcus gallinarum MRx0518 live biotherapeutic product; SER-401: Firmicutes-enriched oral spore-based microbiome therapeutic; MET-4: microbial ecosystem therapeutic 4; ICB: immune checkpoint blockade; EDP1503: Bifidobacterium animalis subsp. lactis live biotherapeutic product; spp.: species (plural); JNJ-64041809: live attenuated double-deleted Listeria monocytogenes immunotherapy; CRC: colorectal cancer; VXM01: oral live-attenuated Salmonella Typhi-based vaccine encoding vascular endothelial growth factor receptor 2; VEGFR2: vascular endothelial growth factor receptor 2.

therapeutic benefit. Thus, the principal conceptual contribution of this framework is the definition of a closed regulatory loop rather than another pairwise biological axis. It links microbial signal generation, neural information processing, tumor microenvironmental remodeling, and tumor-driven systemic feedback within a single mechanistic architecture. This model further generates testable predictions: the biological effect of a microbial signal should depend on its neural processing context, tumors with different innervation patterns may respond differently to the same microbial input, and effective intervention may require simultaneous or sequential modulation of more than one regulatory node. Importantly, the individual components of this framework are not uniformly established across cancer types. Direct electrochemical coupling through AMPAR or NMDAR, activity-dependent NLGN3 signaling, tumor microtube networks, and BDNF-TrkB-associated synaptic plasticity are supported predominantly by studies of glioma and selected brain metastases. In extracranial solid tumors, the evidence more commonly concerns autonomic and sensory neurotransmission, neuroimmune regulation, neurotrophin-driven innervation, and perineural invasion. The gut-neuro-tumor signaling feedback should therefore be regarded as a modular, context-dependent, and hypothesis-generating framework rather than an assertion that every molecular module operates in every solid tumor. In this context, shared refers to recurrent organizational principles, such as bidirectional signaling, neural modulation of immune or stromal cells, and microbial regulation through metabolites or systemic immunity. It does not imply that identical neurotransmitters, receptors, microbial taxa, or downstream pathways are present in every tumor. Tumor-specific implementation of the framework is determined by anatomical innervation, tissue-resident cell populations, receptor availability, microbial ecology, and the evolving immune and metabolic state of the TME. Accordingly, the gut-neuro-tumor signaling feedback should be interpreted as a hypothesis-generating framework that organizes currently fragmented evidence and produces experimentally testable predictions, rather than as a fully demonstrated universal signaling pathway.

Future experimental strategies

Validation of the proposed gut-neuro-tumor signaling feedback requires experimental designs that distinguish direct microbiota-tumor effects from neural-mediated effects and establish temporal and causal relationships among the different compartments. A stepwise strategy should combine controlled microbial perturbation, selective neural manipulation, tumor-type-specific models, and spatially resolved molecular analyses. Firstly, the contribution of the microbiota can be examined using germ-free, antibiotic-depleted, and gnotobiotic animals. Germ-free models provide a stringent approach for testing microbiota dependence, although their developmental, immune, and neurological abnormalities may complicate interpretation. These models should therefore be complemented by antibiotic depletion, recolonization with defined microbial consortia, monoassociation with candidate strains, or supplementation with specific microbial metabolites. FMT from tumor-bearing, treatment-responsive, or treatment-resistant donors can test whether a phenotype is transferable, whereas reciprocal FMT and metabolite-rescue experiments can help distinguish community-level effects from those mediated by individual microbial products. And most importantly, neural mediation should be tested through selective interruption or manipulation of candidate neural pathways. Surgical or chemical vagotomy can assess the contribution of vagal signaling, but its effects on intestinal motility, barrier function, and systemic inflammation require sham-operated and physiological controls. More selective approaches, including branch-specific vagotomy, sympathetic or sensory denervation, receptor blockade, chemogenetic or optogenetic manipulation, neural tracing,

electrophysiological recording, and calcium imaging, may provide greater anatomical and functional resolution. A causal neural intermediary would be supported when disruption of a defined neural pathway attenuates the effect of a microbial perturbation on tumor growth, immunity, or therapeutic response. In the meantime, validation should use orthotopic, spontaneous, or genetically engineered tumor models that preserve tissue-specific innervation and immune architecture. Factorial experimental designs combining microbiota manipulation and neural intervention are particularly important. Spatial transcriptomics, single-cell RNA sequencing, single-cell chromatin profiling, multiplex immunofluorescence, spatial metabolomics, and microbial localization techniques can subsequently define where microbial, neural, immune, and tumor signals converge. These analyses should be paired with direct functional measurements because receptor expression or transcriptional signatures alone do not demonstrate neural activity or signal transmission. Finally, longitudinal integration of metagenomics, metabolomics, proteomics, neural-activity measurements, immune profiling, and tumor phenotyping will be required to establish temporal ordering. Multi-omics associations alone remain correlative and should therefore be combined with perturbation, rescue, and causal-mediation analyses. The strongest support for the proposed framework would require three linked observations: a defined microbial perturbation alters neural activity and tumor behavior, selective neural interruption reduces or abolishes the tumor effect, and microbial recolonization or metabolite rescue restores the phenotype.

Prospects

In addition to offering a conceptual roadmap for linking host microbiota and neural circuitry with the TME, this route represents a multicomponent, druggable system to model the emergence of next stage precision oncology paradigms. In contrast to classical tumor intrinsic targets, the axis comprises a series of hierarchical and spatially separated regulatory nodes that couple microbial metabolites, neurotransmitter receptors, neural circuits, and immune effector pathways in an integrated manner to control tumor behavior in a context dependent fashion. This compositional modularity allows the therapeutic targeting of individual levels along the axis, and thus, therapy can be personalized based on tumor type, neural innervation patterns, microbial composition and host immune status. Of particular note, it is now apparent that effective modulation of this axis need not involve complete inhibition of the pathway but simply recalibration of signal strength, temporal dynamics, and the appropriate target cell. For instance, microorganism metabolite derived interventions might recalibrate neural and immune signaling in ways that do not reach the tumor cells while neuronal modulatory interventions like β adrenergic inhibition or vagal nerve regulation may reprogram the tumor immune milieu rendering it more responsive to immunotherapy. These characteristics make the gut-neuro-tumor signaling feedback unique from classic oncogenic signaling pathways and support its investigation as a potential platform for context-specific interventions, although comparative efficacy and systemic safety remain to be established. From a translational point of view, the further therapeutic exploitation of this axis is expected to be based on integrative patient stratification approaches that entail the simultaneous profiling of microbiome composition with neural activity signature and immune phenotyping. One such strategy could be determining the most dominant regulatory nodes in individual tumors and direct rational combination therapies that concurrently target microbial, neural and immune elements. Several limitations currently restrict validation of the proposed hierarchy. Most studies examine only one or two compartments of the network, use different tumor types and experimental conditions, and measure microbial, neural, immune, and tumor responses at separate time points. Neural activity is also frequently inferred from neurotransmitter levels or receptor expression rather than measured directly. Moreover, microbiota-derived products may reach tumors through circulatory or immune routes without obligatory neural processing, making it necessary to distinguish neural mediation from parallel systemic effects. Future validation will require experiments combining defined microbial or metabolite perturbations with direct neural recording and selective neural manipulation, such as pathway-specific activation, inhibition,

denervation, or receptor blockade. These interventions should be integrated with orthotopic tumor models, longitudinal metabolomics, immune profiling, and spatial or single-cell analyses. Demonstrating that neural manipulation interrupts or modifies the effect of a defined microbial signal on tumor behavior would provide stronger causal evidence for the proposed integrator and amplifier function. Future studies should define the applicability of each neural module using tumor-type-specific experimental systems. Evidence for direct neuron-tumor synapses should ideally combine structural visualization with electrophysiological or calcium-signaling measurements, rather than relying solely on receptor expression. Validation should progress from neuron-tumor co-culture and organotypic models to orthotopic animal models and human spatial or single-cell analyses. Together, this axis not only further develops mechanisms of tumor heterogeneity and resistance but provides a roadmap toward rational design of next generation precision therapies beyond the tumor centric paradigms.

DECLARATIONS

Authors' contributions

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Conceptualization, funding acquisition: Yang X

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

The authors used generative artificial intelligence tools Gemini 3 for language polishing and grammatical refinement during manuscript preparation. The authors carefully reviewed and edited the content to ensure scientific accuracy and take full responsibility for the integrity of the work.

Financial support and sponsorship

The work was supported by National Natural Science Foundation of China (80102012209).

Conflicts of interest

The authors declare that they have no known competing financial interests.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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