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Integrating neuroscience and oncology: neuroimmune crosstalk in the initiation and progression of digestive system tumors

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Abstract

Recent global data show that cancers of the digestive system are responsible for approximately one-third of all cancer-related deaths worldwide, underscoring the urgent need for innovative therapeutic strategies. In this context, emerging findings from neuroscience may unveil new avenues for tackling this pressing clinical problem. Over the past few years, rapid progress in cancer neuroscience has increasingly underscored the contribution of the nervous system to the development and progression of digestive tract tumors. Research has shown that the specialized neural network of the gastrointestinal tract establishes a framework for reciprocal interactions with digestive tract tumors. On this anatomical foundation, our review delves into the functional significance of these interactions, emphasizing the bidirectional regulatory pathways between the nervous system and tumor cells during disease progression and highlighting their intricate crosstalk with the immune microenvironment. In particular, it maps the molecular pathways by which both the central and peripheral nervous systems (PNS) modulate tumor initiation and progression. Moreover, it explains how neurotransmitters and neuroendocrine mediators drive tumor expansion through the activation of canonical oncogenic signaling cascades and the remodeling of the immunosuppressive microenvironment. This review seeks to elucidate the molecular underpinnings of neuro-immune-tumor crosstalk and to synthesize the latest neural-targeted therapeutic approaches. It also examines the principal obstacles that are impeding the clinical implementation of these interventions. By presenting an integrated overview, this work serves as a robust resource to inform future studies on neurobiological mechanisms and the development of novel therapies for gastrointestinal malignancies.

Keywords Cancer neuroscience, Digestive system tumors, Neuroimmune crosstalk, Tumor microenvironment, Neuro-targeted therapy, Neuroendocrine mediators

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Introduction

Recent global data indicate that over 4.8 million new cases of digestive system malignancies, including esophageal, liver, pancreatic, gastric, and colorectal cancers, were reported, leading to approximately 3.2 million deaths, accounting for nearly one-third of all cancer-related fatalities worldwide [1]. This substantial global health challenge highlights the pressing need for innovative therapeutic approaches to combat these cancers. Histopathological studies dating back over one hundred years first documented neural infiltration within the tumor microenvironment (TME) [2], but this observation attracted minimal attention until recent advancements in cancer neuroscience. In recent decades, research on the components of the TME has significantly intensified. During this period, the nervous system has regained prominence as a central area of investigation in oncology, fueling rapid progress in the field of cancer neuroscience. An in-depth understanding of the crosstalk between the nervous system and tumors is crucial for developing novel therapeutic strategies.

Emerging evidence indicates that tumors extensively interact with both local and systemic neural networks, profoundly influencing their growth and progression. Locally, tumor cells and adjacent nerves engage in a bidirectional exchange of neurotransmitters and neuroendocrine mediators within the TME. This interaction promotes the directed growth of nerve fibers into the tumor stroma [3, 4]. In addition, infiltrating nerves release neurotransmitters such as norepinephrine and acetylcholine (ACh), as well as nerve growth factor (NGF). These molecules directly trigger signaling pathways that drive cancer cell proliferation [5, 6]. At the systemic level, the central nervous system (CNS) orchestrates immune surveillance via dedicated brain nuclei and neural pathways. Furthermore, chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis and other neuroendocrine systems. This activation reshapes systemic antitumor immunity through downstream hormonal signaling cascades [7–9]. Collectively, these observations underscore the need to integrate cancer neuroscience with tumor immunology to elucidate the neuroimmune interactions that drive tumor progression. Cancer neuroscience primarily investigates the two-way regulatory crosstalk between tumors and the nervous system. In contrast, tumor immunology focuses on the mechanisms by which immune cells detect tumor antigens and the strategies tumors employ to escape immune surveillance [10, 11]. Integrated analyses indicate that tumor cells create a dynamic regulatory niche within the neuro-immune network by sharing key signaling molecules, such as neurotransmitter receptors and immune checkpoint proteins, and that elucidating this complex phenomenon and its underlying mechanisms is crucial for the development of next-generation therapies.

In this review, we map systemic and local regulatory networks linking the nervous, immune, and tumor compartments to clarify how the nervous system interacts with cancers of the digestive tract, basing our analysis on a detailed understanding of enteric innervation. We also examine the interplay between neural signaling cascades and canonical oncogenic pathways, identifying their shared effector routes. From a translational standpoint, we propose that modulating neural signaling could enhance the efficacy of current immunotherapies; targeting receptors for neurotransmitters and neuroendocrine factors may strengthen clinical responses to immune checkpoint inhibitors. This integrative perspective offers a new framework for designing combination treatments that precisely regulate the neuro-immune-tumor axis.

Anatomical basis of nervous system-digestive system tumor interactions

In vertebrate species, the nervous system comprises two principal components, the central and the PNS. The CNS includes the brain and the spinal cord, while the PNS encompasses all neurons situated outside these regions. The PNS is subdivided into the somatic nervous system and the autonomic nervous system. The autonomic branch consists of the parasympathetic, sympathetic, and enteric nervous systems [12]. Typically, a peripheral nerve contains thousands of bundled axons that branch repeatedly to form intricate networks within their target organs. Autonomic nerve fibers innervate and regulate most internal organs, glands, and blood vessels, thereby preserving physiological homeostasis at rest and during stress. They also aid the restoration of organ structure and function following injury, supporting the concept of "nerve dependence" in tissue regeneration. Recent evidence shows that autonomic activity can drive tumorigenesis; in certain cases, this activity mirrors an uncontrolled variant of the tissue regeneration process [13]. Understanding the patterns of innervation in the digestive system under normal and cancerous conditions is crucial for clarifying neuro-tumor interactions in digestive-system cancers.

Physiological characteristics of digestive system innervation

During neurotransmission, ACh is the principal neurotransmitter at parasympathetic synapses and in sympathetic pre-ganglionic fibers, whereas sympathetic post-ganglionic fibers mainly release norepinephrine. At autonomic ganglia, ACh transmits signals from pre-ganglionic to post-ganglionic neurons by activating cholinergic receptors. The resulting post-ganglionic fibers innervate visceral organs, including the gastrointestinal

tract. Within these tissues, ACh from parasympathetic fibers and norepinephrine from sympathetic fibers bind their respective receptors on epithelial, immune, and stromal cells, thereby modulating cellular activity. Epinephrine released into the circulation by the adrenal glands, together with soluble factors produced in the TME, can also act directly on gastrointestinal target cells.

Visceral afferent fibers provide the main extrinsic sensory input to the gut. These fibers travel alongside autonomic nerves and reach the central nervous system by two routes. Celiac-to-pelvic afferents arising from thoracolumbar dorsal root ganglia ascend chiefly through the sympathetic chain, whereas afferents from lumbosacral dorsal root ganglia follow parasympathetic pathways. Both pathways convey sensory information to the brain via the spinal cord. Vagal afferent cell bodies reside in the nodose and jugular ganglia, and their axons terminate in the nucleus tractus solitarius of the brainstem [14–16].

The enteric nervous system integrates signals from the gut lumen and wall through region-specific circuits composed of intrinsic primary afferent neurons, interneurons, and motor neurons. Together, these circuits regulate intestinal motility, secretion, and vascular tone [14, 17, 18]. Extrinsic neurons also relay sensory signals directly to the sympathetic prevertebral ganglia [18]. Enteric neuron subtypes communicate through several neurotransmitters, including ACh, nitric oxide, and serotonin, and they secrete neuropeptides such as neuropeptide Y, substance P (SP), and vasoactive intestinal peptide. These combined signals maintain gastrointestinal homeostasis and coordinated motility (Figure 1).

Innervation patterns in digestive system tumors

Sympathetic and parasympathetic fibers innervate the pancreas, regulating the endocrine functions of acinar and ductal cells [19]. Compared with healthy tissue, pancreatic ductal adenocarcinoma (PDAC) shows greater nerve density, pronounced neural hypertrophy, and higher norepinephrine levels, suggesting that PDAC cells stimulate axonal growth in their microenvironment [20]. Tumor cells attract nerve fibers by secreting neurotrophic factors such as nerve growth factor, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). These proteins promote axonal extension, guide neuronal wiring, preserve synaptic plasticity, and protect neurons from injury; they can also act autocrinally to increase tumor invasiveness [21]. Perineural invasion (PNI) is detected in 71 to 100% of resected PDAC specimens and is associated with poor clinical outcomes [22].

In gastric cancer, most infiltrating nerve fibers originate from the vagus nerve, and this pattern of innervation

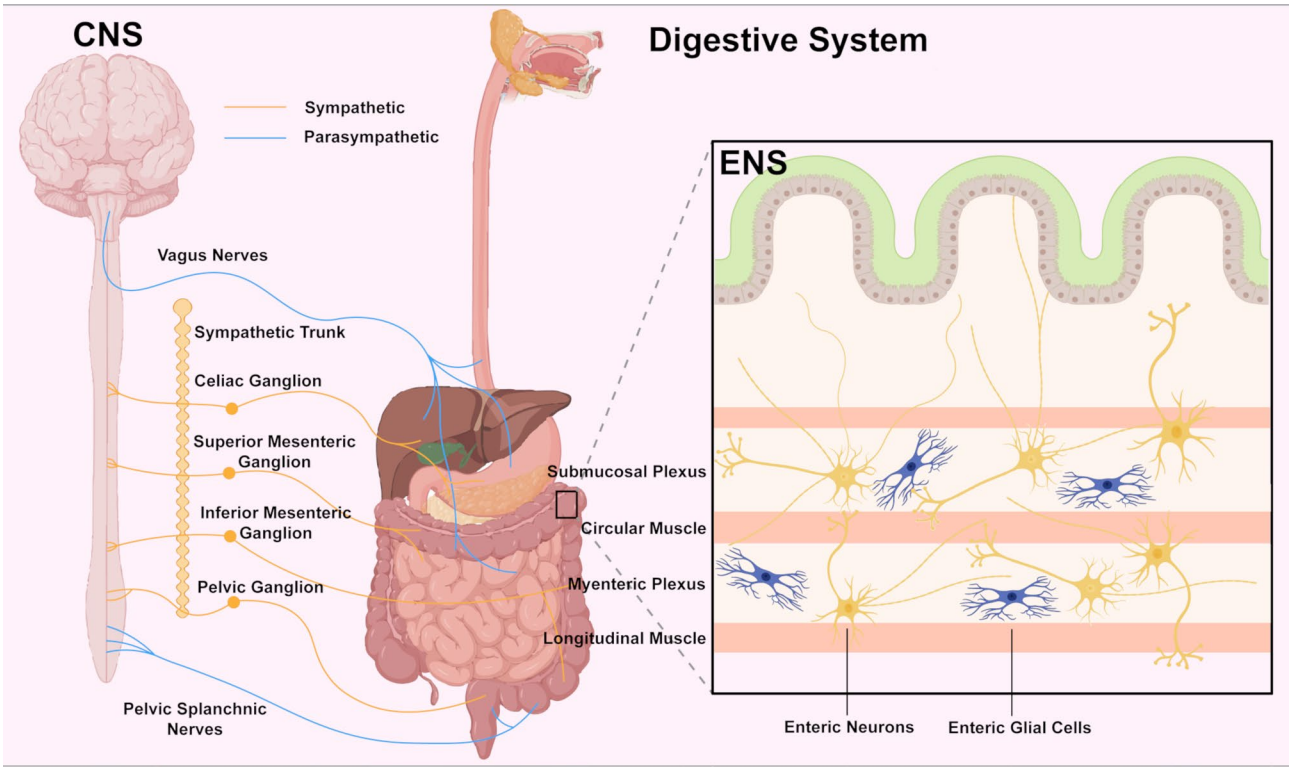

Fig. 1 Innervation characteristics of the digestive system. Schematic diagram illustrating the innervation patterns across distinct organs in the digestive system and detailing the unique features of the enteric nervous system (ENS), thereby establishing an anatomical foundation for understanding the interplay between digestive system tumors and neural networks

strongly influences tumor behavior. In mouse models, surgical vagotomy markedly reduces gastric tumor cell proliferation [23–25], and adequate vagal input is required at every stage of gastric carcinogenesis [25]. A higher density of vagal fibers in the stomach also correlates with more advanced disease [25]. Clinically, about 80% of human gastric cancers arise along the lesser curvature, whereas the greater curvature is affected less often [26, 27]. A similar distribution is seen in the Insulin-Gastrin (INS-GAS) transgenic mouse model of spontaneous gastric cancer [28, 29]. INS-GAS mice show no visible preneoplastic changes before six months of age; they then progress through atrophic and metaplastic phases and develop gastric cancer by twelve months. Detailed mapping of vagal fibers and ganglia in these mice reveals greater neuronal density and larger ganglia along the lesser curvature than the greater curvature [28, 29]. The alignment between this innervation pattern and tumor development in INS-GAS mice has prompted further investigation into the role of neural elements in gastric carcinogenesis.

The intestine receives dense neural input from both intrinsic and extrinsic sources. Intrinsic innervation originates within the ENS, whereas extrinsic innervation reaches the gut through sympathetic and parasympathetic pathways. Experimental and clinical studies show that phenotypic progression in colorectal cancer (CRC), the prototypical intestinal malignancy, is closely linked to alterations in both forms of innervation [30, 31]. Glial cells outnumber neurons in the nervous system by approximately ten to one. These support cells guide neural development and regeneration, maintain axonal integrity, and produce the neural extracellular matrix; they also promote cancer progression [32, 33]. Schwann cells (SCs), which are the glia of extrinsic nerves, occupy about 90% of the perineural space and have become key subjects of research in pancreatic cancer and CRC [34–36]. SCs were first recognized for transmitting nerve signals and repairing neural injury, and they also stabilize the peripheral microenvironment to support neuronal activity. Their contributions within the TME remain incompletely defined. SCs are now regarded as pivotal mediators of PNI, the infiltration of cancer cells into the perineural space, nerve sheath, or adjacent neural structures. PNI represents a distinct pattern of tumor spread that correlates with deeper invasion, broader metastasis, and poorer outcomes in gastrointestinal cancers, including pancreatic, gastric, and colorectal tumors. In CRC, PNI is associated with greater invasion depth, lymphovascular invasion, distant metastasis, and a higher tumor node metastasis (TNM) stage, making it a marker of tumor aggressiveness [37, 38]. Both the presence and spatial distribution of SCs in intestinal tumors strongly influence survival, particularly in stage II and stage III disease [39]. Enteric glial cells (EGCs) form a specialized class of peripheral glia within the ENS [32]. They preserve intestinal barrier integrity, regulate mucosal immune responses, and facilitate tissue repair and regeneration [40]. EGCs are found throughout every layer of the gastrointestinal wall and are most abundant in the myenteric and submucosal plexus ganglia [41]. Although historically understudied, EGCs are receiving increasing attention for their roles in CRC.

Among the nerves supplying the liver, the vagus nerve plays a pivotal role in modulating hepatic function [42–44]. Vagal fibers travel to the liver alongside branches of the common hepatic artery. Some fibers terminate near the hepatic hilum, where they connect with the bile ducts, whereas most continue along the gastroduodenal branches to innervate the gastric antrum, duodenum, and pancreas [45, 46]. Hepatic vagal branches support hepatocyte regeneration [47], regulate glucose metabolism [48], and shape systemic inflammatory responses [49]. Loss of vagal input disrupts both metabolic and immune homeostasis, a disturbance that may foster the initiation and progression of liver disorders, including malignancies [50, 51]. Sympathetic innervation of the liver is highly conserved across species. Although the anatomical distribution of sympathetic fibers varies [42], sympathetic signaling consistently influences hepatic metabolism, especially glucose turnover. Neural inputs also affect tumor progression and clinical outcomes in hepatocellular carcinoma (HCC) [52]. In HCC, nerve diameter, density, and proximity to tumor cells, including the presence of PNI are key determinants of metastasis and patient survival. Larger and denser nerves predict poorer prognosis [53]. Elevated expression of tyrosine hydroxylase (TH) and vesicular acetylcholine transporter (VAChT), markers of sympathetic and parasympathetic nerve density respectively, is associated with vascular invasion, advanced stage, and reduced overall survival. TH expression also independently predicts HCC recurrence [54].

Patterns of innervation in esophageal carcinoma and their clinicopathological relevance remain incompletely defined. In a cohort of 260 esophageal carcinoma specimens (40 paired lymph-node metastases and 137 adjacent non-neoplastic samples), neural distribution was mapped by immunohistochemistry. Neural infiltration appeared in 38% of tumors and was significantly more common in squamous cell carcinoma ($P = 0.04$). PNI, identified when tumor cells encircle or penetrate nerve fibers, occurred in 12% of cases and was linked to poorer patient survival ($P = 0.04$). Further analyses showed that neural elements express key NGF receptors, namely tropomyosin receptor kinase A (TrkA) and the NGF receptor. Elevated NGF expression in tumor cells was significantly associated with nerve presence ($P = 0.02$)

[55]. These findings indicate that neural distribution is a characteristic feature of esophageal carcinoma, probably driven by tumor-derived NGF, which promotes nerve infiltration and tumor progression. Additional studies are warranted to clarify neural distribution patterns in this malignancy.

Communication modalities between the nervous system and digestive system tumors

Recent evidence shows that the nervous system does more than transmit signals. It can initiate digestive-tract tumors, drive their progression, and shape antitumor immunity through distinct anatomical and molecular routes. These actions unfold on three progressively finer levels: systemic cross-organ crosstalk, cellular interplay within the TME, and precise molecular signaling events. Together, these tiers provide a complete view of the neuro-immune-tumor network.

The nervous system is a key regulator of internal homeostasis. Central signals from the sympathetic and parasympathetic branches of the autonomic nervous system coordinate the production, renewal, and movement of immune cells in primary and secondary lymphoid organs, such as the bone marrow, spleen, and lymph nodes [56]. Norepinephrine released by sympathetic fibers guides hematopoietic stem cells to their bone marrow niches and later promotes their mobilization into the bloodstream [57, 58]. A recent study shows that the body-brain axis uses specific vagal fiber subtypes to amplify or dampen peripheral inflammation, thereby fine-tuning immune activity [59]. Therefore, the nervous system is indispensable for systemic immune balance and for shaping the microenvironment within lymphoid organs. In addition, the nervous system controls the occurrence and progression of digestive system tumors by modulating the immune system via the neuro-endocrine axis, circadian rhythms, and the gut-brain axis. For instance, under stress conditions, sympathetic nerves release norepinephrine, which acts on tumor blood vessels and tumor-associated macrophages, promoting angiogenesis and suppressing anti-tumor immunity [60]. Circadian rhythm disruption affects cancer progression by regulating various cancer hallmarks, including DNA damage, apoptosis, cell cycle and senescence [61, 62], proliferation [63–65], metabolism [66], and genomic instability and mutations [61, 67, 68], which may also reduce sensitivity to anti-tumor drugs. Dysbiosis of the gut microbiota and microbiota-derived metabolites, such as neurotransmitters, short-chain fatty acids, and amino acids, not only alter the TME of the central nervous system and influence brain tumors [69–74] but also directly induce intestinal inflammation and carcinogenesis, thus promoting colorectal cancer progression [71–73, 75, 76]. This integrated network underpins effective immune surveillance while also creating conditions that allow gastrointestinal tumors to evade immune detection.

Nerve fibers infiltrate the TME of digestive tract cancers and create a dynamic network that links neurons, tumor cells, and immune cells. Sympathetic terminals secrete norepinephrine and epinephrine, these catecholamines enhance tumor proliferation and invasion through β-adrenergic receptors and shift dendritic cells (DCs), macrophages, and T lymphocytes toward an immunosuppressive state. By contrast, stronger vagal activity can curb tumor growth. These findings suggest that separate neural circuits exert pathway-specific control over cancer behavior. Additionally, tumors such as PDAC secrete neurotrophic factors that induce peripheral nerve regeneration and axonal infiltration into the tumor, forming a “tumor-nerve” interactive scaffold that promotes tumor cell proliferation and invasion [77]. All cells secrete exosomes, which function as molecular signaling mechanisms, with their contents determined by their cell of origin [78]. In this context, researchers speculate that neurons may enhance local intercellular communication and remotely facilitate tumorigenesis by establishing metastatic niches through exosome secretion, thereby acting as mediators of carcinogenesis. Communication between digestive system tumor cells and nerves occurs through neuronal exosomes, resulting in tumor innervation and neuro-modulation of the TME. Moreover, digestive system tumor cells also secrete exosomes containing axon-guidance molecules, thereby promoting neuronal axonogenesis towards the tumor. This further supports the critical role of cancer-derived extracellular vesicles in axonogenesis [79]. Thus, therapeutic strategies aimed at interfering with cancer-derived exosome release or their functional blockade may represent a novel approach for cancer treatment.

Neural elements modulate tumor cells and their stroma by releasing neurotransmitters, neurotrophic factors, and neuropeptides. Many digestive-tract cancers overexpress nerve growth factor and its receptor Trk, which stimulate tumor proliferation and intensify perineural invasion (PNI) [80, 81]. Neuropeptide U (NPU) and its receptor are found on both cancer cells and other TME components, allowing NPU to remodel the local niche and foster tumorigenesis [82]. These ligand-receptor pairs act as key molecular hubs that relay signals and drive downstream responses in the dialogue between neural elements and the TME. In addition to remote secretion, neuron-tumor synapse-like structures formed in central nervous system tumors such as gliomas drive tumor progression, and the resulting depolarization of glioma cell membranes stimulates tumor cell proliferation. The number of synapses formed between neurons and gliomas is regulated by the BDNF-TrkB signaling pathway. Elimination of BDNF secretion in the brain microenvironment

or loss of TrkB expression in gliomas significantly inhibits the progression of brain tumors such as gliomas [83]. Currently, such synapse-like structures have rarely been reported in digestive system tumors, future research is needed to elucidate molecular signaling between digestive tumors and enteric intrinsic neurons to identify additional anti-cancer strategies.

Overall, the nervous system promotes the initiation and progression of gastrointestinal cancers through three linked levels: modulation of systemic immunity, coordination of neuro and TME interactions, and activation of specific ligand receptor pathways. Defining the roles of individual neural circuits and molecular mediators in tumor immunity at each disease stage will lay the groundwork for future neuroimmune focused therapies.

Bidirectional regulatory networks between the nervous system and digestive system tumors

CNS functional architecture and key pathways regulating digestive system tumors

The CNS comprises the brain and spinal cord and is the primary hub for sensory integration, motor control, and homeostatic regulation. Through neuroendocrine routes such as the HPA axis, it governs stress responses, energy metabolism, and immune surveillance. By releasing neurotransmitters like norepinephrine and dopamine, the CNS communicates in both directions with the immune system and thus shapes tumor initiation and progression [84]. Beyond these classical neuroendocrine and immune pathways, recent evidence shows that neural circuits limited to specific brain regions and their functional nuclei can directly promote the development and growth of gastrointestinal cancers.

Tumor regulation by specific brain regions

Disruption of specific brain regions is closely linked to cancer. The suprachiasmatic nucleus (SCN) is the master clock for human circadian rhythms. In many patients with cancer, SCN controlled rhythms become disturbed, possibly because of tumor related stress or intrinsic SCN dysfunction [85]. Persistent circadian disruption increases cancer risk [86–88]. Laboratory studies show that light exposure at night dampens SCN activity and alters the circadian control of immune genes, changes that favor tumorigenesis [89–91]. Epidemiological data concur, as night shift workers have higher rates of prostate, colorectal, and lung cancers [88, 92, 93]. The SCN also drives the rhythmic release of melatonin from the pineal gland through γ aminobutyric acid (GABA) neuronal pathways (Fig. 2) [94]. Melatonin expands effector T-cell numbers and reduces immunosuppressive regulatory T cells [95]. In the circulation, melatonin binds its receptors on immune cells and prompts the secretion of proinflammatory and immunostimulatory cytokines, including interleukin-1 (IL-1), IL-6, IL-12, tumor necrosis factor (TNF), and interferon-γ (IFN-γ) [96]. This cytokine cascade strengthens immune activity. Consequently, SCN disruptions that dampen melatonin rhythms may promote tumorigenesis by weakening both innate and adaptive immune responses [97].

Orexigenic neurons in the arcuate nucleus (ARC) and the lateral hypothalamic area form a network that controls energy metabolism via coordinated signals from the paraventricular nucleus (PVN), the ventromedial hypothalamus (VMH), and the dorsomedial hypothalamus (DMH) [98, 99]. This circuit contributes to gastrointestinal tumor development. Activation of orexin receptor type 1 (OX1R) by orexin-A or by the antagonist almorexant induces apoptosis in pancreatic cancer cells [100], whereas elevated serum leptin promotes tumor progression by suppressing hypothalamic orexin release [101, 102]. Environmental enrichment (EE) increases BDNF expression in the ARC, VMH, and DMH. The resulting rise in BDNF inhibits leptin secretion by adipocytes and enhances adiponectin production through HPA axis activation and sympathetic outflow. Because leptin stimulates cell proliferation while adiponectin inhibits it, this adipokine shift reduces tumor growth and increases apoptosis and this effect has been observed in CRC and melanoma research models [103]. Targeting the BDNF and leptin signaling axis between the brain and peripheral tissues may therefore offer new approaches to cancer therapy [103].

Glucocorticoid (GC) regulation via the HPA axis

Clinical data increasingly link chronic stress to poorer outcomes in digestive tract cancers. A pooled analysis of individual-level data from 16 large prospective cohorts found that chronic stress significantly raises mortality risk in CRC, worsening patient prognosis [104]. Similar findings have been reported in pancreatic cancer [105]. Chronic stress activates PVN neurons in the hypothalamus and sustains signaling via the HPA axis. This ongoing activation drives prolonged systemic release of GCs (Figure 2) [106].

GCs promote tumorigenesis by activating the glucocorticoid receptor (GR). In its unbound state, GR restrains rat sarcoma viral oncogene homolog (Ras) signaling. When GCs bind, the GC-GR complex releases GR from Ras and translocates to the nucleus. Free Ras then engages the mitogen-activated protein kinase (MAPK) cascade, driving tumor initiation and invasion [8]. GR also regulates cell-cycle progression: dexamethasone-activated GR increases cyclin-dependent kinase 1 (CDK1) transcription APC MIN, which accelerates cancer cell proliferation. Clinical data show that loss of either GR or CDK1 impairs metastatic colorectal cancer growth, highlighting the GC-GR-CDK1 axis as a

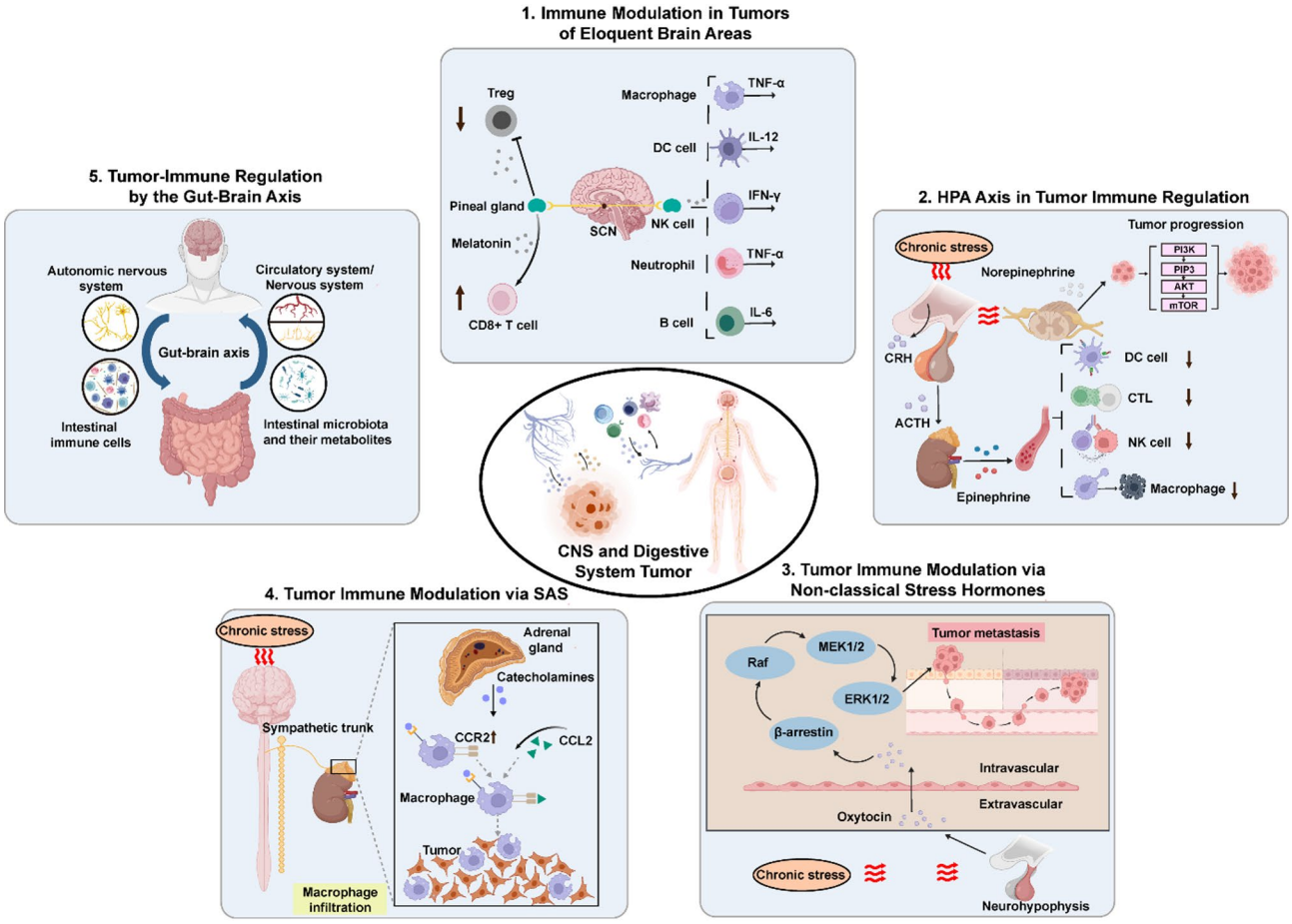

Fig. 2 Interactions between the CNS and digestive system tumor. (1) The immunomodulatory role of specialized functional brain regions within the CNS. (2) The regulation of anti-tumor immunity by the classic HPA axis. (3) The modulation of tumor behavior and phenotype by non-classical stress hormones. (4) The immune modulation of SAS. (5) The regulatory pathway mechanisms of the gut-brain axis

therapeutic target in CRC and potentially other gastrointestinal tumors [9] Moreover, GCs induce epithelial and mesenchymal transition (EMT) by activating the Ras/c-Jun N-terminal kinase (JNK) cascade [107], triggering activation of the Ras/c-Jun N-terminal kinase (JNK) cascade. This shift elevates transforming growth factor β (TGF-β), vimentin, Notch-1 and SRY-box transcription factor 2 (SOX-2) while reducing E-cadherin expression. Together, these changes enhance cancer cell self-renewal and accelerate tumor progression [107].

In addition to their direct effects on cancer cells, GCs shape tumor initiation and progression by modulating antitumor immune populations through the GR. GR activation enhances regulatory T cell and myeloid-derived suppressor cell (MDSC) activity, impairs DC cell maturation and antigen presentation, weakens $CD8^+$ T lymphocyte and natural killer (NK) cell cytotoxicity, and polarizes macrophages toward an M2 phenotype. It also skews cytokine networks by suppressing key antitumor mediators such as IL-12 and IFN-γ [108]. Moreover, GR promotes immune evasion by inhibiting T cell receptor (TCR) signaling via lymphocyte-specific protein tyrosine kinase (LCK) and FYN proto-oncogene, Src family tyrosine kinase (FYN) [109]. GR-induced thymic involution further reduces circulating T cell numbers, facilitating tumor escape and accelerating cancer growth and spread [105].

Regulatory functions of non-classical stress hormones

Non-classical stress hormones contribute substantially to tumor progression. Chronic stress leads to sustained activation of the HPA axis and increases corticotropin-releasing hormone (CRH) secretion from the hypothalamus. CRH then modulates the activity of oxytocin neurons, enhancing oxytocin release from the posterior pituitary into the bloodstream. Under chronic stress, oxytocin also drives melanoma metastasis through β-arrestin 2-dependent activation of the extracellular signal-regulated kinase (ERK) cascade (Fig. 2) [110]. Peripheral dopamine exerts antitumor effects. In ovarian carcinoma, by binding dopamine receptor D2 (DRD2), dopamine inhibits tumor proliferation and lowers microvascular density,

Table 1 Summary of interactions between CNS and digestive system tumor

Interaction type	Main regulatory factors	Signaling pathways/ mechanisms	Immune effector modulation	Biological impact/ outcome	Potential therapeutic strategies
Specialized brain region regulation	Melatonin; Leptin; BDNF.	SCN dysregulation disrupts melatonin rhythm affecting immune genes; BDNF upregulation inhibits leptin, increases adiponectin, modulating tumor growth and apoptosis.	Low melatonin reduces effector T cells and increases Tregs; BDNF regulates leptin/adiponectin balance, enhancing antitumor factors and suppressing protumor factors.	Circadian rhythm disruption increases tumor risk; interventions on the energy metabolism axis suppress proliferation and promote apoptosis.	Light therapy and melatonin supplementation to restore rhythm; BDNF upregulation or leptin receptor antagonists to modulate the energy metabolism axis.
HPA axis-glucocorticoid regulation	GC; GR.	Stress activates the HPA axis, raising GC; the GC-GR complex translocates to the nucleus, activating RAS/MAPK and upregulating CDK1 and EMT-related genes.	GC-GR enhances Treg and MDSC suppressive functions, inhibits DC maturation and $CD8^+$ T cell/NK cell activity, promoting immune evasion.	Persistent GC elevation drives proliferation, invasion, and metastasis while impairing antitumor immunity.	GR antagonists or CDK1 inhibitors to block proliferative signaling.
Non-classical stress hormone regulation	Corticotropin-releasing hormone (CRH); Oxytocin; Peripheral dopamine (DA).	CRH and oxytocin activate ERK signaling to promote metastasis; dopamine via D2 receptor lowers cAMP and Src, inhibiting tumor proliferation and angiogenesis.	Oxytocin promotes metastasis; dopamine enhances NK cell activity and cytokine secretion, inhibiting tumor growth.	Stress-induced fluctuations in oxytocin and dopamine levels bidirectionally regulate tumor progression.	Intervention with ERK pathway inhibitors; dopamine agonists or D2 receptor agonists to bolster antitumor immunity.
SAS adrenergic regulation	Epinephrine/ norepinephrine (E/NE)	Catecholamines activate β-adrenergic receptors and upregulate CCL2/CCR2, promoting monocyte/macrophage recruitment; α_2 receptors feedback regulate release intensity.	Catecholamines suppress NK cells and promote MDSC recruitment; β-blockers can restore NK function and reduce MDSC.	SAS signaling drives enhanced migration and metastasis; β-blockers can reverse this effect.	β-adrenergic blockers antagonize catecholamine signaling; α_2 agonists provide feedback inhibition of catecholamine release.
Bidirectional brain-gut axis regulatory network	Enteric nervous system; Vagus nerve; Microbial metabolites.	The CNS regulates gut immunity via the HPA axis and ANS; microbial metabolites feedback through the ENS and vagus nerve; oxytocin neurons act on the gut microenvironment via the celiac ganglia-superior mesenteric ganglion (CG-SMG) pathway.	CNS signals and microbial metabolites enhance $CD8^+$ T cell infiltration and DC/Th1 activity, synergistically suppressing tumors.	Brain-gut axis interactions significantly influence digestive tract tumor initiation and progression, representing potential therapeutic targets.	Probiotics or short-chain fatty acid supplementation to reshape the microbiota; vagus nerve stimulation (VNS) to boost gut immunity; oxytocin pathway modulators targeting the gut microenvironment.

countering the pro proliferative impact of chronic stress. Dopamine also decreases intracellular cyclic adenosine monophosphate (cAMP) and blocks Src kinase activation by norepinephrine and vascular endothelial growth factor (VEGF) [111]. The antitumor effects of dopamine in digestive system tumors have been less studied; however, given its antitumor activity in other cancers, we hypothesize that dopamine may also exert antitumor effects in these tumors, which requires further investigation to confirm. Chronic stress also activates the HPA axis and elevates hypothalamic CRH secretion. CRH then modulates dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra, reducing central dopamine production. Stress also engages the sympathetic nervous system to alter peripheral dopamine release. These combined effects weaken dopamine's anti-tumor functions.

Adrenergic regulation by the sympatho-adrenal system (SAS)

Beyond its effects on the HPA axis, chronic stress promotes tumor progression by activating the SAS. Epinephrine and norepinephrine are released primarily to counter external stressors and maintain homeostasis. In cancer, however, these catecholamines drive both tumor initiation and disease progression.

Preclinical studies show that chronic stress-induced activation of the SAS accelerates tumor progression. In pancreatic cancer models, β-adrenergic receptor agonists reproduce stress-related tumor promotion, while β-blockers block this effect [112]. Restraint stress increases hepatic metastases of colon cancer cells, and β-blockers markedly reduce metastatic spread [113]. In vitro, β_2-adrenergic receptor (β_2-AR) agonists significantly enhance gastric cancer cell migration versus controls [114]. In a chronic restraint model, non-β-adrenergic agonists reveal that α_2-adrenergic signaling, via an autoreceptor feedback loop, suppresses sympathetic catecholamine release and thereby dampens the tumor-promoting impact of β-adrenergic signaling in digestive tract malignancies.

Mechanistic investigations show that activation of the SAS under chronic stress reshapes tumor cell behavior and phenotype mainly by altering immune cell functions. In lung metastasis models, chronic stress significantly enhances tumor cell engraftment, accompanied by increased C-C motif chemokine receptor 2 (CCR2) expression in both pulmonary stromal cells and monocyte/macrophage subsets, reflecting elevated β-adrenergic signaling. Together, these findings suggest that stress-released catecholamines recruit monocytes and macrophages via the C-C motif chemokine ligand (CCL) 2 -CCR2 axis, thereby promoting pulmonary metastasis (Figure 2) [115, 116]. Whether the recruitment of monocytes and macrophages via the CCL2-CCR2 axis under chronic stress promotes metastasis in digestive system tumors warrants further investigation. Under surgical stress, SAS activation reduces both the number and cytotoxic activity of NK cells in spontaneous and transplant tumor models. Treatment with β-blockers restores NK cell-mediated cytotoxicity [117]. These findings illustrate that chronic stress-SAS signaling modulates NK cell activity and thus contributes to tumor progression.

Bidirectional signaling within the brain-gut axis

The brain-gut axis comprises the CNS, the autonomic nervous system (ANS), and the gastrointestinal microbiota [118]. At the outset of digestive system tumorigenesis, bidirectional communication along the brain-gut axis establishes an integrated response to malignant growth. The CNS shapes intestinal immune defenses via the HPA axis and the ANS. In turn, microbial metabolites such as short chain fatty acids, neuroactive mediators like serotonin, and gut hormones convey information back to the CNS through the ENS, vagal afferents, or the bloodstream [119]. In a CRC model, catecholaminergic neurons in the ventrolateral medulla (VLM) accelerate tumor progression by suppressing $CD8^+$ T cell activity [120]. Oxytocin neurons in the hypothalamic PVN communicate with the CRC microenvironment through the oxytocin-celiac-mesenteric ganglion signaling axis and, by modulating HPA axis activity, also inhibit tumor progression (Fig. 2) [121]. The above studies collectively demonstrate that the brain influences the development of gastrointestinal tumors by regulating the immune system.

On the other hand, the gastrointestinal microbiota [122], as a key component of the brain-gut axis, plays an important role in the initiation and progression of gastrointestinal tumors, especially colorectal cancer. Metabolites produced by the gastrointestinal microbiota can accumulate in the TME and act as ligands for specific receptors as well as modulators of certain protein activities, thereby regulating signaling pathways and ultimately influencing gene expression within cells and cytokine levels in the TME. For example, butyrate produced by fermentation of dietary fiber by gut microbiota promotes regulatory T cell (Treg) differentiation and inhibits T helper 17 cell (Th17) differentiation via G protein-coupled receptors on macrophages and dendritic cells [123, 124]. In the colonic TME, Th17 cells exacerbate chronic inflammation and inflammatory diseases [125, 126], whereas Treg cells suppress chronic inflammation. Therefore, butyrate inhibits colonic inflammation and impedes colorectal cancer progression. Additionally, butyrate inhibits histone deacetylases (HDACs), reducing macrophage inflammatory responses and preventing colorectal cancer onset [127]. Beyond its anti-inflammatory effects, short-chain fatty acids produced by gut microbiota enhance anti-tumor immunity via interaction with free

Table 2 Summary of interactions between CNS and tumor immune microenvironment effects

Interaction Type	Affected Immune Cell Types	Main Regulatory Mechanisms	Tumor Immune Microenvironment Effects	Biological Impact
Specialized brain region regulation	Effector T cells; Tregs.	SCN dysregulation disrupts melatonin secretion rhythm; ARC/BDNF-leptin axis remodels energy metabolism.	Reduced melatonin leads to decreased effector T cell activity and increased Tregs; BDNF-regulated leptin/adiponectin balance enhances antitumor effects.	Weakened immune surveillance; increased tumor proliferation, decreased apoptosis.
HPA axis-glucocorticoid regulation	Tregs; MDSCs; DC; $CD8^+$ T; NK cells.	Chronic stress elevates GC levels; GC-GR complex activates RAS/MAPK, CDK1, and EMT-related genes.	GC-GR pathway enhances suppressive functions of Tregs and MDSCs, inhibits DC maturation, and weakens $CD8^+$ T and NK cell functions	Enhanced immunosuppression; increased tumor invasion and metastasis.
Non-classical stress hormone regulation	NK cells.	CRH and oxytocin activate ERK signaling to promote metastasis; dopamine via D2 receptor reduces cAMP and Src to inhibit proliferation and angiogenesis.	Oxytocin promotes metastasis; dopamine enhances NK cell activity and cytokine secretion, inhibiting tumor growth.	Bidirectional regulation of tumor progression via fluctuating hormone levels.
SAS adrenergic regulation	NK cells; Monocytes/Macrophages.	Catecholamines activate β-adrenergic receptors and upregulate CCL2/CCR2, recruiting monocytes/macrophages; α2 receptors provide feedback inhibition.	Catecholamines suppress NK cell activity and promote MDSC recruitment; β-blockers restore NK function and reduce MDSCs.	SAS signaling promotes tumor migration and metastasis; β-blockers can counteract these effects.
Bidirectional brain-gut axis regulatory network	$CD8^+$ T cells; DC; Th1 cells	CNS modulates gut immunity via HPA axis and autonomic nervous system; microbial metabolites feedback through enteric nervous system and vagus nerve; oxytocin neurons influence gut microenvironment via celiac and superior mesenteric ganglia.	CNS signals and microbial metabolites enhance infiltration and activation of $CD8^+$ T cells and DC/Th1 cells.	Brain-gut axis critically affects digestive tract tumor initiation and progression, serving as a potential therapeutic target.

fatty acid receptor 2 (FFAR2). When FFAR2 is knocked out, dendritic cells become overactivated and produce IL-27, which further impairs immunity against colorectal cancer by depleting $CD8^+$ T cells [128]. Short-chain fatty acids in the colon also inhibit epithelial secretion of the pro-inflammatory cytokine IL-8 to suppress colorectal cancer, though the precise mechanisms require further investigation [129]. Although short-chain fatty acids possess strong anticancer properties, in certain contexts they may promote cancer progression. When common oral bacteria Helicobacter pylori F7-1 and altered Schaedler flora (ASF) colonize the intestines of germ-free mice, H. pylori-derived short-chain fatty acids bind to FFAR2, increasing intestinal cancer risk and promoting IL-17 expression, thereby fostering a pro-inflammatory environment prior to tumor formation. This complex effect of gastrointestinal microbiota metabolites cautions researchers that their function may be closely linked to the surrounding environmental context. For instance, inosine was once considered an inhibitor of T helper 1 cells (Th1) differentiation; however, in the presence of exogenous IFN-γ and co-stimulation, inosine promotes Th1 differentiation [130, 131]. Therefore, the application of gut microbiota and its metabolites in radiotherapy, chemotherapy, and immunotherapy for gastrointestinal tumors remains a challenging task. Beyond traditional strategies that disrupt the gut microbiota with antibiotics, new microbiota-based approaches are under development, including dietary modifications, fecal microbiota transplantation, and brain-gut axis interventions, with targeting key enzymes in gut microbiota metabolism also representing potential novel strategies.

This table summarizes the main interaction types between the CNS and gastrointestinal tumors, including for each type the main regulatory factors, signaling pathways/mechanisms, immune effector modulation, biological impact/outcome and potential therapeutic strategies. The table illustrates the connections among key elements within the CNS-immune regulation-gastrointestinal tumor network.

This table summarizes the main types of CNS interactions with the digestive system tumor immune microenvironment and, for each type, lists the affected immune cell types, main regulatory mechanisms, tumor immune microenvironment effects, and biological impact. It illustrates how the CNS specifically modulates immune cells within the digestive system tumor immune microenvironment to influence tumor initiation, progression, and metastasis.

Feedback regulation of the CNS by digestive system tumors

Digestive tract tumors such as gastric cancer and CRC secrete neurotrophic factors (e.g., NGF, BDNF), which

promote local nerve ingrowth and establish a neural niche that supports tumor progression [132]. This aberrant neural remodeling transmits tumor-derived signals to the CNS via a sympatho-sensory feedback circuit, resulting in chronic activation of the HPA axis and intensified neuroinflammatory processes in affected brain regions [133, 134]. Persistent HPA axis hyperactivation and neuroinflammation amplify systemic and local immunosuppression and may induce cognitive deficits and emotional disturbances. These changes further accelerate tumor progression and spread, creating a self-reinforcing cycle.

PNS-digestive system tumor crosstalk

The PNS connects the CNS to peripheral organs. It consists of three main divisions: autonomic, somatic, and enteric. PNI is a key pathological feature in digestive system tumor progression. PNI occurs when malignant cells invade perineural spaces or surround nerve fibers. This allows tumor cells to access neurotrophic factors like NGF, gaining a survival advantage. This invasive process creates a three-dimensional network linking peripheral nerves, cancer cells, and immune cells. Within this niche, the neurotransmitter norepinephrine and various cytokines create a dynamic regulatory environment. These molecular signals influence digestive system tumor development by acting directly on malignant cells and altering the immune landscape of the TME. Understanding the communication pathways between neural components, tumor cells, and immune cells in the digestive system TME will provide the basis for new cancer therapies targeting neural regulation.

PNS-mediated tumor cell regulation in the tumor immune microenvironment

Evidence shows that sympathetic nervous system signaling within the TME drives early tumor development [135]. Adrenergic fibers signal through norepinephrine release. Their receptors include α and β classes, most of which activate downstream pathways. In contrast, the α_2-adrenergic receptor acts as an autoregulatory brake that terminates signaling upon activation. Studies demonstrate that adrenergic pathways significantly promote malignant behaviors in digestive system tumors including gastric [114, 136] and pancreatic cancer [137]. This outcome may occur because adrenergic receptors promote immune deficiencies within the TME, thus facilitating cancer progression. For example, upon β_2-AR activation, $CD8^+$ T cells reduce GLUT1 receptor expression, thereby suppressing the metabolic activity of activated T cells [138]. Meanwhile, activation of adrenergic receptors can reshape the proportions of various T cell subsets. β_2-AR activation on $CD4^+$ T cells upregulates Foxp3 expression and increases the number of Treg [139, 140]. It also promotes the conversion of Th1 cells to T helper 2 cells (Th2), which have pro-tumorigenic effects. β-AR activation can inhibit macrophage secretion of IL-6, IL-1, and TNF-α, inducing an immunosuppressive state [141]. Adrenergic receptors also affect dendritic cell maturation, promoting an immature phenotype and weakening their capacity to activate $CD8^+$ T cells, thereby negatively regulating $CD8^+$ T cell-mediated antitumor immunity [142]. Notably, adrenergic signaling effects vary across gastrointestinal malignancies. In pancreatic cancer, sympathetic fiber stimulation of β_2-AR enhances ERK and cAMP response element-binding protein (CREB) phosphorylation, increasing NGF mRNA expression [137]. This leads pancreatic cancer cells to secrete more NGF, driving sympathetic nerve growth and infiltration. This creates a vicious cycle accelerating tumor progression [137]. In HCC, higher sympathetic fiber density correlates with worse patient survival [54, 143]. Conversely, gastric cancer [144] and CRC [145] show better clinical outcomes with increased sympathetic fiber density and β-adrenergic receptor expression. Additionally, β_2-AR expression directly correlates with malignancy markers including higher tumor grade and invasiveness [146]. Mechanistic studies reveal that nonselective β-blocker propranolol (PRO) inhibits gastric cancer progression by suppressing the nuclear factor kappa B (NF-κB)-VEGF/matrix metalloproteinase-2/9 (MMP-2/9)-cyclooxygenase-2 (COX-2) axis [147]. This paradox stems from dynamic interactions between neural innervation and tumor heterogeneity, including variations in tumor types, receptor subtypes, and other factors, collectively termed the neuro-tumor niche. Analyzing sympathetic nerve density, adrenergic signaling, and tumor genomics together may help predict innervation-driven mechanisms. Sympathetic regulation exhibits heterogeneous effects in gastrointestinal tumors, where targeting single receptors risks disrupting niche homeostasis. System-level approaches are needed to elucidate these complex interactions (Figure 3).

ACh, the primary parasympathetic neurotransmitter, signals through two receptor families: nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs). In digestive tract cancers, both receptor types show altered expression and promote cancer cell proliferation, motility, and survival [148]. Studies indicate that combining gastrectomy with vagotomy or using pharmacological denervation suppresses gastric cancer development and progression [25]. Cholinergic receptor muscarinic 3 (CHRM3) is overexpressed in gastric tissue and promotes tumor growth through two mechanisms: stimulating the epidermal growth factor receptor (EGFR) cascade to drive proliferation [149], and enhancing tumor cell motility to facilitate metastasis [150]. CHRM3 also modulates tissue stem cell functions,

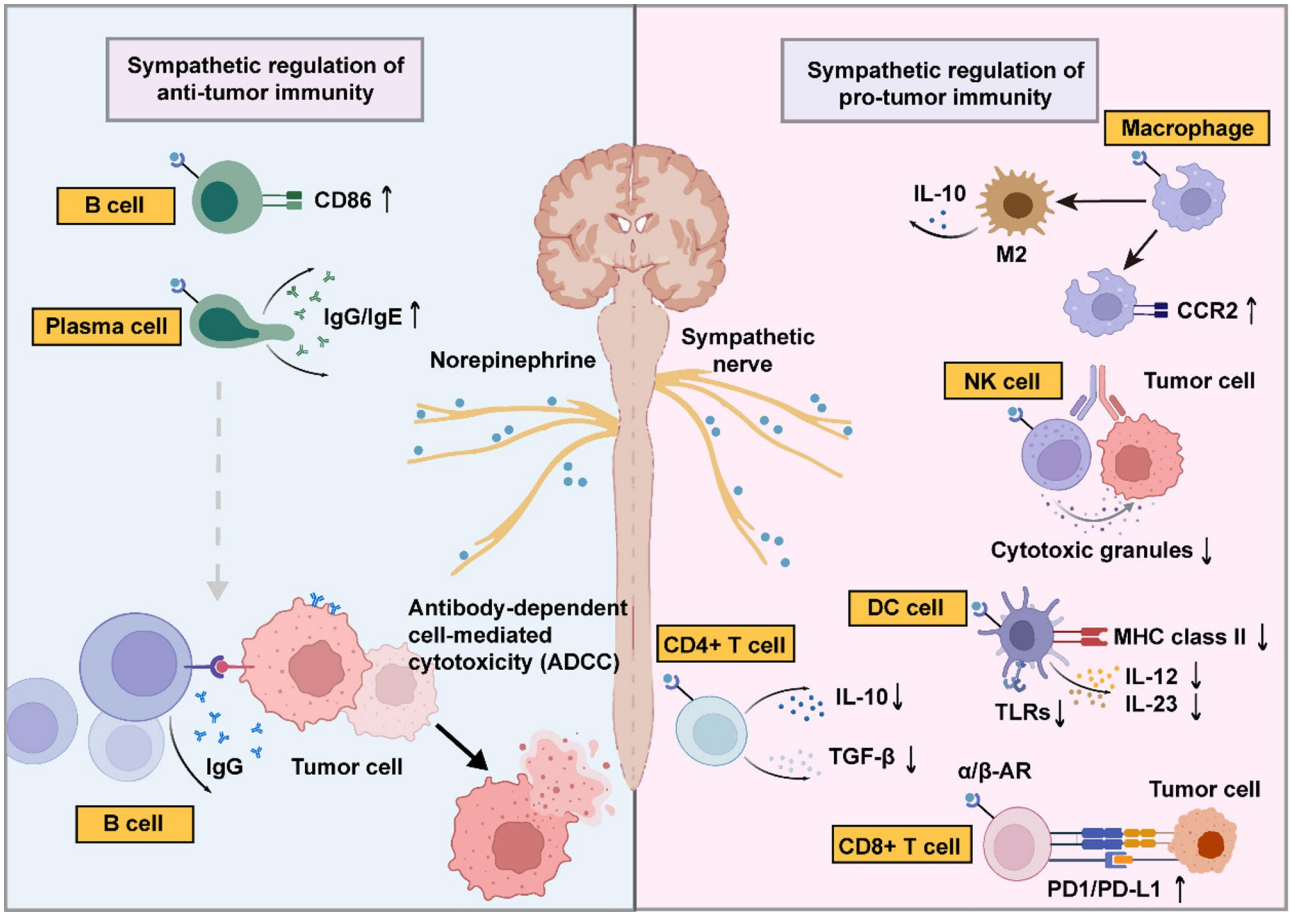

Fig. 3 Sympathetic nervous system-immune cells interactions in the TME. Schematic diagram illustrating the differential immunomodulatory effects of the sympathetic nervous system on various immune cells within the digestive system tumor immune microenvironment, where the left side represents anti-tumor immunoregulation and the right side represents pro-tumor immunoregulation

supporting both epithelial regeneration and tumor initiation [151–153]. Additionally, CHRM3 activates yes-associated protein (YAP) in the Hippo pathway. Activated YAP promotes gastric cancer progression via Wnt signaling [24, 154, 155], highlighting the CHRM3-YAP axis as a therapeutic target for vagal ACh-dependent gastric cancer. Gastrointestinal Dclk1^{+} tuft cells increase local ACh through choline acetyltransferase (ChAT) expression, though their exact oncogenic pathways remain unclear [24]. In colorectal cancer (CRC), the ACh-CHRM3 axis similarly influences tumor development. CHRM3 deletion in Apc^{Min} mice reduces intestinal tumor number and size [156]. Chemically induced colon cancer models show decreased proliferation and fewer/smaller tumors in CHRM3-deficient mice [157]. CHRM3 drives CRC progression by regulating downstream signaling [158]. The α7- and α9-nAChR subtypes are significantly overexpressed in CRC [159, 160], promoting proliferation and inhibiting apoptosis through calcium-dependent autocrine signaling [161]. Nicotine stimulation of α7-nAChR activates both MAPK and JAK2 pathways, increasing digestive system tumor cell metastasis [161, 162]. These findings suggest that targeting both nAChRs and their signaling networks could provide new treatments for patients resistant to MAPK or JAK2 inhibitors (Figure 4).

The ENS can regulate its own signal transduction, thereby affecting gastrointestinal homeostasis, promoting physiological alterations, and subsequently contributing to gastrointestinal diseases, including gastrointestinal tumors [32, 163]. Previous research on gastrointestinal tumors often overlooked the role of the ENS. Recent studies increasingly demonstrate that enteric neurons and enteric glial cells actively communicate with tumor cells via paracrine signaling [24, 25, 164–166]. There is also evidence indicating that the ENS plays a role in the initiation and progression of CRC [167, 168]. Increased cholinergic innervation observed in late-stage CRC is associated with poor prognosis, which has been attributed to peripheral cholinergic nerves [145]; however, the abundant cholinergic neurons within the gut may also promote CRC progression. Additional evidence supporting the role of the ENS in CRC includes a decreased risk

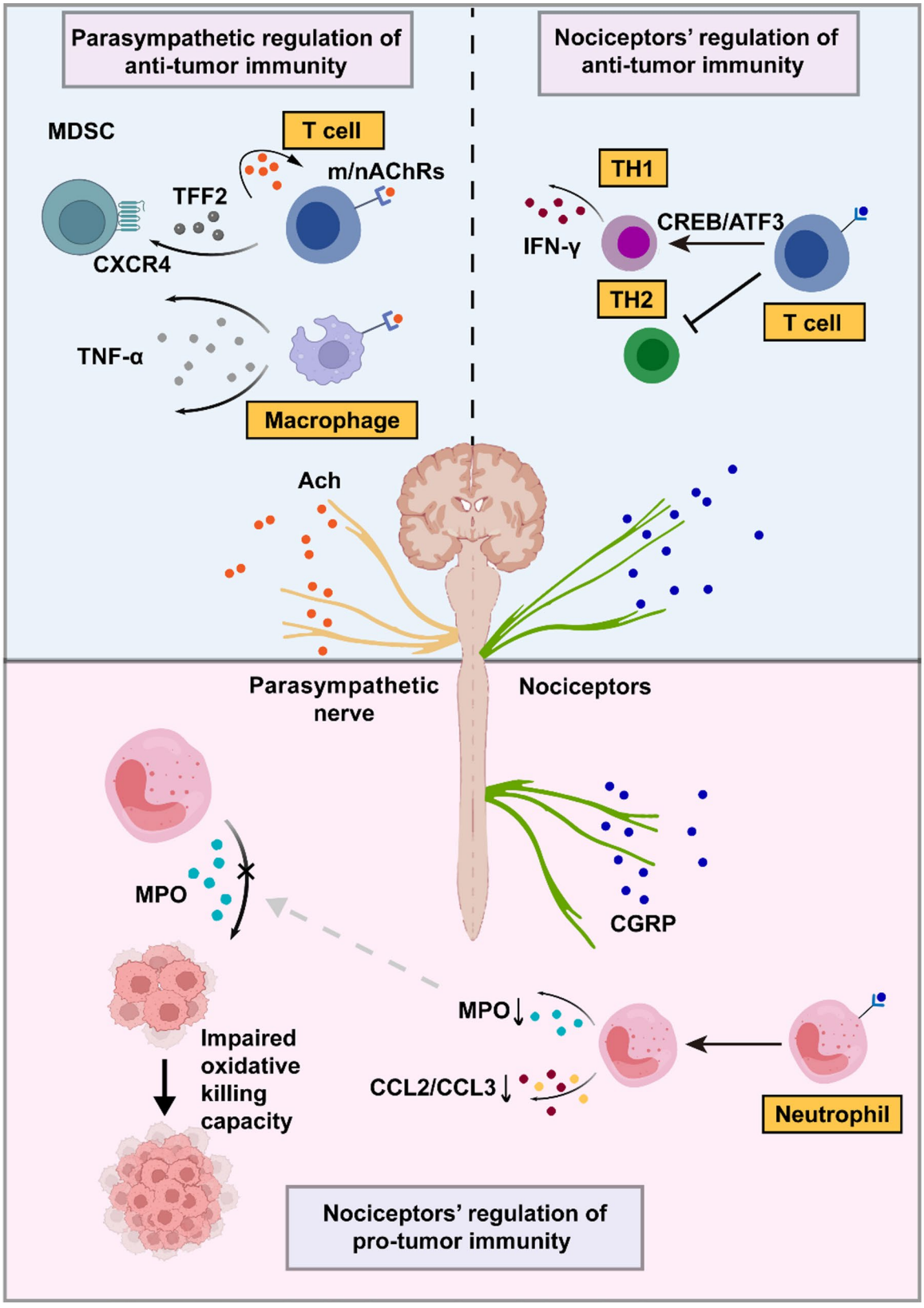

Fig. 4 Parasympathetic nervous system and nociceptors-immune cells interactions in the TME. Schematic diagram illustrating the immunoregulatory roles of the parasympathetic nerves and nociceptors in the tumor immune microenvironment of the digestive system. The top left depicts the antitumor modulation by the parasympathetic nerves. The top right depicts the antitumor immune regulation by nociceptors. The bottom depicts the protumor immune modulation by nociceptors

of CRC in patients who have undergone colonic denervation [169] and animal studies demonstrating reduced CRC incidence following chemical neuronal ablation in rats [170]. Paradoxically, intestinal neurons in CRC have been found to decrease the expression of netrin-1, a protein known to promote intestinal tumorigenesis [171]. Furthermore, research has reported evidence of tumor epithelial cells anchoring to and migrating along enteric neuronal fibers, highlighting the potential role of the ENS in guiding CRC migration [172]. Although research into the role of the ENS in gastrointestinal tumors is still at an early stage and the precise cellular and molecular mechanisms remain unclear, understanding these processes will undoubtedly provide substantial benefits for future therapeutic translation.

Nociceptors in intestinal sensory neurons detect harmful stimuli, triggering protective visceral pain reflexes. However, their role within the gastrointestinal TME remains unclear. It is reasonably hypothesized that nociceptors may promote the development of an immunosuppressive state within the TME. Recent research shows that in gastric cancer, nociceptors form synapse-like connections with tumor cells [173]. Through this neuron-tumor interaction, sensory neurons release calcitonin gene-related peptide (CGRP). CGRP activates downstream pathways that substantially increase gastric cancer cell proliferation and metastatic potential. Subsequent studies showed that blocking CGRP receptors disrupts neuron-tumor connections, significantly reducing gastric cancer cell growth in mice [173]. In PDAC, nociceptors promote tumor progression by interacting with cancer-associated fibroblasts (CAFs) and inhibiting NK cell-mediated immune surveillance. This study revealed that nociceptors engage in bidirectional communication with CAFs via CGRP and NGF signaling, reducing IL-15 expression in CAFs and consequently impairing NK cell infiltration and cytotoxic function [174]. In melanoma, nociceptors can directly enhance the exhaustion of cytotoxic $CD8^+$ T cells, thereby limiting their ability to clear tumor cells [175]. Additional studies indicate that nociceptors facilitate $CD8^+$ T cell exhaustion and increase MDSC infiltration; targeting IL-6 secreted by nociceptors may reverse this immunosuppressive microenvironment [176]. Recent studies indicate that nociceptors promote interactions between DCs and $CD8^+$ T cells in autoimmune diseases [177]; whether a similar mechanism exists in tumors remains to be further investigated. These findings suggest a new therapeutic strategy targeting neural circuits in gastric and other gastrointestinal cancers (Figure 4).

Within the TME, neural components regulate malignant and immune cell behavior while directly interacting with cancer stem cells (CSCs), influencing the local niche. Neural signals also regulate CSC maintenance and activity, underscoring their role in CSC homeostasis. The Wnt, Notch, and Hedgehog pathways form the main network controlling CSC self-renewal. Neural signaling mediators directly regulate these critical pathways. Specifically, muscarinic M3 receptor (M3R) activation stimulates Wnt signaling, driving gastric CSC proliferation and expansion [24, 25]. In KRAS-mutant PDAC, vagal activation suppresses CSC stemness, impeding tumor progression [178].

PNS-immune cell interactions within the tumor immune microenvironment

Within the TME, the PNS shapes immune homeostasis to bidirectionally influence cancer cell behavior. Neutrophils, monocytes, NK cells, and T lymphocytes express adrenergic receptors [179–181]. Different α- and β-adrenergic receptor subtypes mediate diverse regulatory effects on these immune cells within the TME. Immune cells also express nAChRs and mAChRs. Areas with greater parasympathetic innervation show elevated immune checkpoint receptor expression, suggesting cholinergic tone influences checkpoint regulation. Notably, targeted activation of intratumoral parasympathetic fibers reduces programmed cell death protein 1 (PD-1) levels on tumor-infiltrating lymphocytes [182]. This mirrors clinical data showing worse outcomes in patients with reduced parasympathetic innervation. Vagotomy associates with increased incidence and mortality in gastric cancer and CRC [183], possibly due to denervation-impaired thymic lymphocyte egress reducing immune surveillance [184]. These findings demonstrate peripheral nerves directly control immune cell activity through neurotransmitters and regulate immune cell trafficking and activation systemically. Identifying molecular circuits governing PNS-immune crosstalk in the TME will establish fundamental principles for developing neural signaling-targeted anticancer therapies.

T cell Adrenergic signaling affects different T cell populations differently. β-adrenergic stimulation inhibits $CD8^+$ T cell proliferation and cytotoxicity while enhancing Treg immunosuppressive function [185]. Studies show the β-blocker PRO reduces PD-1 levels on $CD8^+$ T cells in stress-linked tumors (Figure 3) [186], similar to the checkpoint reduction after selective sympathectomy [182]. Notably, tumor denervation increases IFN-γ in $CD4^+$ and $CD8^+$ T cells, boosting cytotoxicity and improving outcomes [182]. In a pancreatic cancer model which is resistant to immune checkpoint blockade (ICB), combining β-blockers with ICB boosts $CD8^+$ T cell responses and promotes tissue-resident memory T cell formation and persistence [187]. Importantly, β_1-adrenergic activation drives $CD8^+$ T cell exhaustion, which β_1-blockers prevent [187]. β_2-adrenergic receptor (β_2-AR) knockout

mice show more intratumoral effector CD8⁺ T cells, lower PD-1, and higher effector-to-Treg ratios [186], suggesting sympathetic fiber density drives tumor progression.

T cells regulate immunity via cholinergic signaling. T cells synthesize and secrete ACh [188, 189], forming an autocrine loop that modulates their activation and effector functions. In the spleen's immunosuppressive niche rich in MDSCs, vagal signaling induces memory T cells to release anti-inflammatory trefoil factor family 2 (TFF2). TFF2 engages C-X-C chemokine receptor type 4 (CXCR4) to inhibit MDSC proliferation, disrupting immunosuppression and limiting tumor growth (Figure 4) [190].

CGRP released from nociceptors modulates T-cell subset differentiation. CGRP binds the receptor complex of receptor activity-modifying protein 3 (RAMP3) and calcitonin receptor-like receptor (CALCRL). This enhances Th1 commitment while suppressing Th2 differentiation through the CREB/activating transcription factor 3 (ATF3) signaling cascade (Figure 4) [191]. As a higher Th1/Th2 ratio enhances antitumor immunity, these findings identify a new target for modulating neuro-immune crosstalk [191].

B cell Research shows different stress types with distinct catecholamine patterns differentially regulate IgG secretion. Acute stress increases IgG production by promoting plasma cell differentiation [192], while prolonged stress reduces IgG synthesis by inhibiting B-cell activation (Figure 3) [192]. Chronic stress minimally affects IgM secretion [193], suggesting separate regulatory pathways for immunoglobulin isotypes. In B cells, β_2-AR activation elevates CD86 expression, enhancing antigen presentation and increasing IgG1 and IgE secretion [194, 195]. This "enhanced function-suppressed proliferation" paradox reveals the complexity of adrenergic B cell regulation, requiring further study incorporating dynamic microenvironmental changes [196]. This paradox of increased functional activity alongside reduced proliferation reveals the complex nature of adrenergic B cell regulation and emphasizes the need for studies incorporating dynamic microenvironmental changes.

Monocytes/Macrophages β-adrenergic pathway activation regulates monocyte and macrophage functions. β-adrenergic stimulation promotes macrophage polarization toward the M2 phenotype [197], creating an immunosuppressive TME. Studies show the β-agonist isoproterenol (ISO) increases monocyte CCR2 expression, promoting recruitment into pre-metastatic niches (Figure 3) [115]. Catecholamines also drive monocyte migration via the CCL2-CCR2 axis, facilitating tumor metastasis [115, 116]. Notably, α_2-adrenergic agonists exhibit potent antitumor activity in immunocompetent mice, including ICB-resistant and humanized patient-derived xenograft (PDX) models [198]. This activity involves multiple mechanisms: dexmedetomidine enhances macrophage antigen presentation and CD8⁺ T cell activation [198], while selective agonists improve monocyte function to block tumor immune escape [199]. These findings offer new strategies for targeting specific adrenergic receptors to remodel antitumor immunity.

Cholinergic receptor activation similarly regulates macrophage immune functions. Reduced mucosal ACh levels exacerbate dextran sulfate sodium (DSS)-induced colitis in depression models by altering macrophage polarization [200, 201]. Diminished cholinergic signaling promotes pro-inflammatory macrophage polarization [202]. Critically, vagus nerve stimulation (VNS) activates the α7-nAChR on splenic macrophages, significantly reducing pro-inflammatory cytokines like TNF-α (Figure 4) [203]. This provides molecular evidence for neuroimmune regulation of inflammation. Thus, cholinergic pathways modulate macrophage polarization between pro- and anti-inflammatory states through receptor-mediated mechanisms, suggesting oncology treatment strategies.

DC cells α_2-adrenergic receptor activation inhibits DC cell immune function by impairing antigen processing and presentation, and reducing migratory capacity [204]. This signaling also suppresses IL-12 and IL-23 production, further compromising DC-mediated immunity (Figure 3) [205]. CGRP regulates DC activity through two mechanisms: suppressing IL-12 synthesis (impeding Th1 commitment) and reducing CCR2, CCL2, and CCL12 expression (diminishing chemotaxis) [206] Additionally, CGRP upregulates antimicrobial genes (Cfp, Clec10a, Cd300lf, Ifitm1, Ifitm2, Ifitm6) to promote a protective DC phenotype without causing inflammation. This immunomodulation involves non-canonical p38 kinase signaling, balancing defense and immunopathology risks. These dual effects impair DC antitumor immunity and provide molecular evidence for neuro-immune crosstalk in tumor progression.

Neutrophils CGRP modulates neutrophil activity through two mechanisms. First, CGRP inhibits neutrophil myeloperoxidase (MPO) activity, reducing oxidative bactericidal capacity [207]. Second, in meningeal niches, CGRP signaling suppresses macrophage-derived chemokines (CCL2, CCL3, CXCL10), impairing neutrophil recruitment to inflammatory sites (Figure 4) [208]. These combined effects weaken neutrophil-driven immunity, creating a paradoxical state that promotes both inflammation and immunosuppression. This increases infection susceptibility and facilitates tumor immune escape.

NK cells NK cells express functional β-adrenergic receptors, and β_2-AR signaling impairs their activity, representing a key pathway by which stress accelerates tumor growth [209]. Norepinephrine binding to β_2-AR on NK cells inhibits degranulation and suppresses release of antitumor cytokines such as IL-2 (Figure 3) [210]. Simultaneously, β_2-AR activation reduces NK cell adhesion to vascular endothelium, which paradoxically increases motility and promotes deeper tissue infiltration [211]. This combination of functional suppression and enhanced migration alters NK cell distribution within the TME and weakens effective immune surveillance.

MDSCs MDSCs are a principal immunosuppressive cell population tightly controlled by adrenergic signaling. When β-adrenergic receptors engage, hematopoietic stem cells differentiate into monocytic (M-MDSC) and polymorphonuclear (PMN-MDSC) subsets [212]. Furthermore, receptor activation reshapes the local metabolic milieu which is marked by lactate buildup and triggers immunosuppressive mediator secretion, augmenting MDSC function [213]. The neuro–myeloid interaction network highlights key molecular targets of stress-mediated tumor immune evasion.

PNS-vascular and lymphatic crosstalk in the tumor immune microenvironment

Within the tumor vascular microenvironment, adrenergic nerve fibers surround blood vessels, especially arterioles and capillaries, as well as components of the lymphatic network. Recent studies show that adrenergic signaling precisely controls endothelial metabolism. Activation of the β_2-AR maintains aerobic glycolysis to promote angiogenesis, whereas genetic ablation of β_2-AR shifts metabolic flux toward oxidative phosphorylation, causing angiogenic defects and slowing tumor growth [214–216]. This regulatory network provides a foundation for therapies that disrupt neuro-vascular crosstalk to block tumor expansion. Furthermore, stimulation of β_3-AR on tumor cells increases release of IL-6, IL-8, vascular endothelial growth factor, and fibrinogen-like protein 2, driving inflammation and neovascularization within the TME [217, 218].

Adrenergic neural inputs regulate lymph flow and lymphocyte egress in the lymphatic system. In experimental tumor models, lymphatic network remodeling depends on adrenergic signaling via lymphatic endothelial β_2-AR [219], creating pathways for tumor cells to escape. Similar to their role in angiogenesis, sympathectomy reduces lymphangiogenesis and curbs cancer invasiveness [220].

Multifaceted PNS regulation of stromal cells within the tumor immune microenvironment

Within the TME, stromal cells contribute to both treatment resistance and tumor progression. Adrenergic signaling induces cancer cells to upregulate inhibin βA, which then triggers collagen synthesis by CAFs. Excess collagen forms a physical barrier that prevents therapeutic agents from reaching tumor cells, promoting both tumor growth and treatment resistance. β-Adrenergic receptor antagonists block this CAF phenotypic switch [221]. However, it is unclear whether neural blockade always yields benefit. Although CAFs were once seen solely as drivers of tumor progression, recent data reveal that, like immune cells, they have diverse functions during tumorigenesis and can sometimes act in ways that counter conventional expectations [222]. Nonselective removal of CAFs or broad inhibition of their functions can eliminate tumor-suppressive extracellular matrix components and beneficial CAF subpopulations, impairing antitumor responses [223, 224]. In this evolving context, the exact role of neural inputs remains to be clarified.

Adrenergic innervation also regulates adipocyte remodeling in the TME. At the onset of cancer cachexia, catecholamines acting on β-adrenergic receptors transform white adipose tissue into a brown-like, energy-dissipating phenotype, which accelerates cachexia [225]. However, no experimental evidence to date links this adipose remodeling directly to tumor progression. In adipose-rich tumors, a subset of cancer-associated adipocytes secretes various adipokines that affect tumor initiation, growth, metastasis, and cachexia [226]. Via BDNF-mediated signaling, the CNS influences tumor-innervating adrenergic fibers, reducing leptin release from adipocytes and thereby suppressing tumor cell proliferation [103].

Multidimensional PNS regulation of other tumor immune microenvironment components

Neurogenic inflammation in the TME is a key driver of malignant transformation. In pancreatic cancer models, minimal activation of pancreatic afferent nerves triggers neurogenic inflammation during the precancerous pancreatic intraepithelial neoplasia (PanIN) stage, while neuropeptides such as SP further accelerate progression to PDAC [5]. Mechanistic studies show that neonatal capsaicin administration selectively eliminates pancreatic sensory neurons, blocking the neuro-inflammatory-tumor signaling axis and prolonging survival in PDAC model mice proportionally to the dose [6]. These findings provide crucial experimental evidence that targeting neurogenic inflammation can impede malignant transformation.

Tumor-induced remodeling of the PNS

Digestive system tumors can reverse-modulate the PNS by releasing neuroendocrine factors such as NGF. This promotes nerve fiber ingrowth into the TME and establishes tumor innervation. Such neural infiltration amplifies the impact of adrenergic fibers on tumor behavior and directly drives tumor cell proliferation and invasion through neural signaling pathways. Moreover, tumor-induced chronic inflammation and stress impair PNS function, disrupt immune homeostasis, and create a self-sustaining cycle that accelerates tumor progression and metastasis.

In summary, the PNS profoundly affects both initiation and progression of digestive system tumors via two main routes: modulation of the immune microenvironment and direct neural signaling. Simultaneously, tumors secrete neurotrophic factors that promote neural ingrowth and induce epigenetic changes in neural plasticity, creating a self-sustaining cycle of immune evasion. This bidirectional regulatory network highlights the pivotal role of the PNS in tumor metabolic adaptation and immune editing and provides an interdisciplinary framework for neuro-immune combination therapies, notably through targeting neurotransmitter receptors, interrupting neuro-tumor synapses, and modulating neurogenic inflammation.

Crosstalk between classic tumor signaling pathways and the neuro-immune axis

Mechanisms in the neuro-immune-tumor network operate upstream of canonical oncogenic pathways. Defining the connections between this network and established tumor-associated signaling cascades could provide a solid rationale for co-targeting both pathways and their neural signaling components, especially in patients who do not respond to inhibitors of traditional oncogenic routes [227].

Canonical tumor-associated signaling pathways include the MAPK cascade, the phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K-AKT-mTOR) axis, the p53 network, the Wnt/β-catenin pathway, the Notch pathway, and Hippo signaling pathway. Contemporary neuro-oncology paradigms move beyond a tumor-cell-centric model to a dynamic, tripartite regulatory network that integrates neural, immune, and canonical pathways. Within this framework, multidimensional crosstalk uncovers novel docking sites for neuro-interface-targeted therapies and offers strategies to overcome resistance to inhibitors of traditional oncogenic routes (Fig. 5).

Integration of tumor and neural signaling molecule receptors

Trk receptor signaling

The Trk receptor family mediates neurotrophin signaling, governing neural development, cell survival, and tumorigenesis. TrkA, TrkB, and TrkC are activated by NGF and BDNF. Nearly half of pancreatic cancer patients exhibit elevated Trk expression [80]. NGF or BDNF binding triggers oncogenic cascades such as MAPK and PI3K/AKT, promoting tumor cell survival and proliferation. In some cancers, high TrkB expression drives tumor progression via these pathways [228]. Activation of the neurotrophin receptor kinase 1 (NTRK1)-encoded TrkA receptor initiates the MAPK cascade, a signaling axis essential for neuronal differentiation and growth that also drives malignant tumor proliferation [81]. Cholinergic signaling via the vagus nerve raises NGF levels, activating the Wnt pathway and driving gastric tumorigenesis [24]. NTRK1 signaling further engages CREB, a transcription factor controlling neuronal development, survival, synaptic plasticity, and neurotransmission gene expression [229]. CREB overexpression induces programs that fuel proliferation, confer apoptosis resistance, stimulate angiogenesis, facilitate immune evasion, and promote epithelial-mesenchymal transition, correlating with poor prognosis [230–233]. Inhibiting CREB, NGF, or NTRK1 can disrupt multiple downstream cascades driving gastrointestinal tumor progression. However, their broad activity profiles raise concerns about off-target effects and toxicity, complicating clinical development.

Catecholamine receptor signaling pathways

Stress acts as an independent carcinogen by promoting genomic instability through dysregulated hormone signaling. Persistent β_2-AR activation induces DNA double-strand breaks, as shown by increased phosphorylated histone H2AX (γ-H2AX) levels [234]. Moreover, defective DNA damage repair alters mutation frequencies in key oncogenes, including cyclin-dependent kinase inhibitor 2 A (CDKN2A), myelocytomatosis oncogene (MYC), cyclin D1 (CCND1), and EGFR [235, 236]. Genomic instability driven by adrenergic signaling is a hallmark of digestive tract tumorigenesis.

Within the TME, adrenergic signaling promotes malignancy by coordinating various cell types. Activation of β_2-AR on endothelial cells induces pathological angiogenesis via the hypoxia-inducible factor (HIF)-1α/VEGF pathway [237, 238]. This aberrant vessel growth is fully blocked by combining β-blockers with HIF inhibitors [238]. Adrenergic regulation of immune function varies by receptor subtype: innate immune cells primarily express α_1, α_2, and β_2-AR, while adaptive lymphocytes depend on β_2-AR. This tripartite network, linking neuroendocrine signals, receptor activation, and the immune

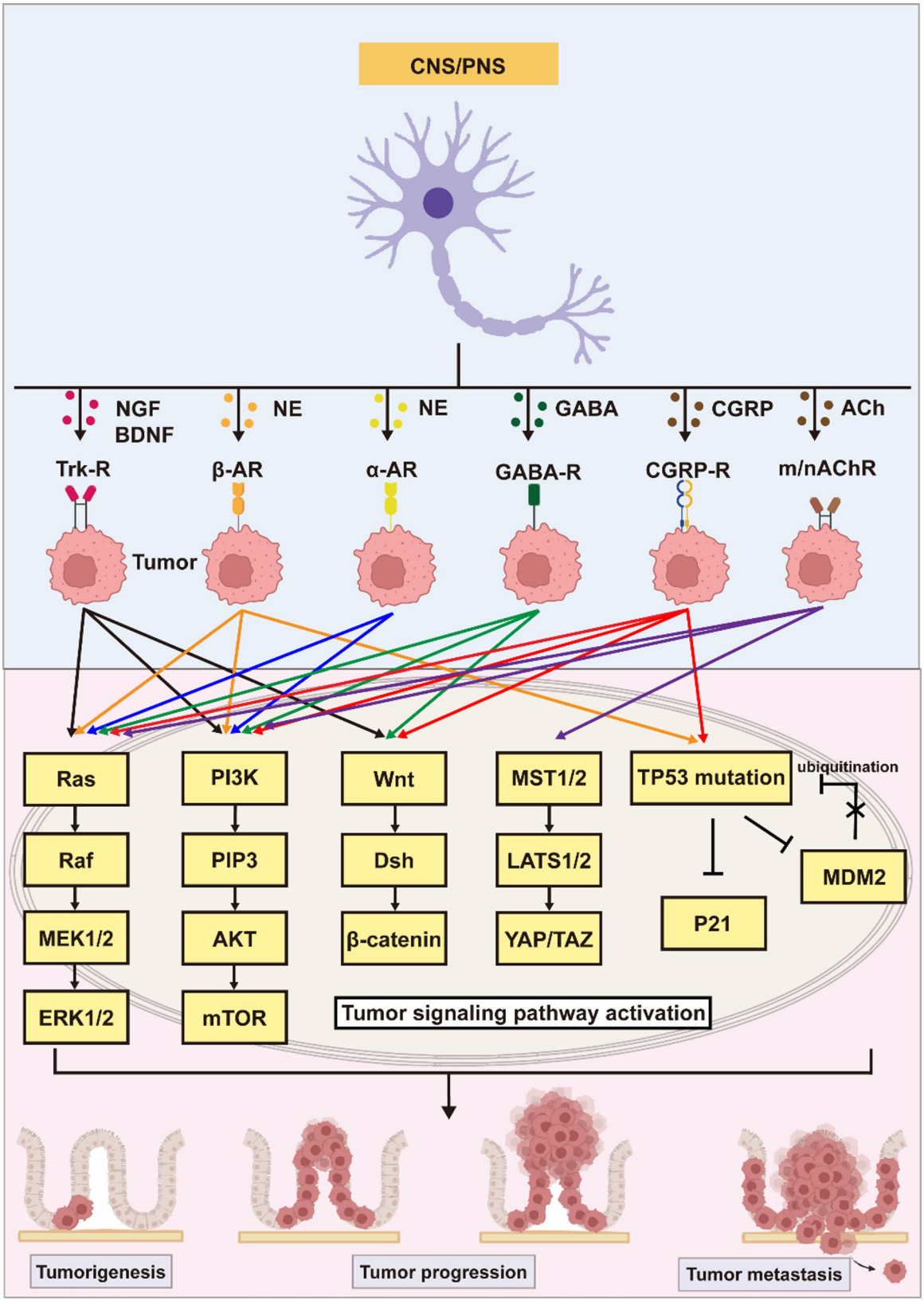

Fig. 5 Summary of integration between classic tumor signaling pathways and neural signaling pathways. Schematic diagram illustrating interactions between multiple neural signaling pathways and distinct oncogenic tumor signals: a single neural pathway can activate several oncogenic signals, and conversely, a single oncogenic signal can be activated by multiple neural pathways, highlighting the complexity of nerve-tumor signal communication

microenvironment, provides a molecular basis for designing multi-targeted interventions to counteract stress-induced carcinogenesis.

GABA receptor signaling pathways

GABA, as a major inhibitory neurotransmitter in the CNS, acts via ionotropic $GABA_A$ receptors, $GABA_A$-ρ receptors (formerly $GABA_C$ receptors), and metabotropic $GABA_B$ receptors [239, 240]. The GABA signaling pathway exerts bidirectional control over tumor progression, mediated by differential expression of its receptor subtypes. In digestive system tumors, both pancreatic and liver cancer cells exhibit upregulated $GABA_A$ receptor expression. $GABA_A$-positive tumors are typically more aggressive, and activation of these receptors stimulates tumor cell proliferation [241, 242]. In contrast, $GABA_B$ receptor expression is diminished in HCC and pancreatic cancer cells [242, 243]. Activation of these receptors suppresses tumor cell growth [244], and baclofen, a prototypical $GABA_B$ agonist, has been demonstrated to inhibit HCC proliferation [242]. Glutamate decarboxylase 67 (GAD67), which synthesizes GABA, and GABA transaminase, which degrades GABA, are key enzymes in GABA metabolism and have both been linked to tumor malignancy. Elevated GAD67 expression correlates with advanced clinical stage and poor prognosis in various solid tumors [245]. Reduced GABA transaminase expression in liver cancer patients further supports GABA's role in promoting malignant phenotypes [246]. Recent investigations, mirroring findings in other neuro-immune axes, have uncovered a regulatory function for $GABA_A$ receptors in the tumor immune microenvironment [247]. In CRC mouse-derived model, B cell-derived GABA drives monocytes to become anti-inflammatory macrophages that secrete IL-10 and suppress $CD8^+$ T cell cytotoxic function [247].

Other neural signaling pathways

CGRP released by nociceptors plays a critical immunoregulatory role. Its receptor-mediated immunosuppressive pathway in leukocytes depends on adenylyl cyclase-activated protein kinase A (PKA), which upregulates the inducible cAMP early repressor (ICER), inhibits NF-κB activity, and reduces pro-inflammatory mediators such as TNF-α [248]. CGRP-mediated immunosuppression has been observed in various pathological contexts and can sometimes be harmful. Nociceptors form a diverse group of neuronal subtypes, each defined by distinct morphology, electrophysiological and stimulus-response profiles, molecular markers, and peripheral innervation patterns [249]. Further research is needed to identify which neuropeptides from specific nociceptor subtypes drive neuro-immune crosstalk. Integrating these findings into predictive functional networks using recent computational advances could yield valuable insights.

Neuroligin-3 (NLGN3) is a candidate mitogenic factor released by peritumoral neurons and is essential for synapse formation, functional modulation, and intercellular communication in the nervous system. Recent evidence shows that NLGN3 also affects the TME. Once secreted, NLGN3 is cleaved by a disintegrin and metalloproteinase 10 (ADAM10) and activates the PI3K-mTOR pathway, promoting tumor cell proliferation [250–253].

Neural regulation of immune cell functions

Immune cells such as T cells, NK cells, and macrophages in the TME are shaped not only by tumor-derived signals but also by neural inputs. Because immune and neural cells share receptors, altered activation of neural receptors can change immune cell infiltration patterns (for example, T cells) and increase exhaustion levels [187] It can also drive upregulation of immune checkpoint molecules such as PD-1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) in tumor-infiltrating lymphocytes [187].

Furthermore, neural networks in the tumor stroma modulate the local metabolic environment, including lactate, glutamate, and choline levels. These alterations indirectly activate the PI3K-AKT and AMP-activated protein kinase (AMPK) pathways to reprogram immune cell metabolism, resulting in either immunosuppressive or immunostimulatory states within the tumor [254].

Emerging therapeutic strategies targeting neural regulation in digestive system tumors

Denervation therapy

Given the key role of nerves in tumor initiation and progression, both surgical denervation and localized chemical denervation with botulinum toxin type A have attracted attention. Preclinical and clinical studies show that denervation significantly reduces the incidence and growth of gastric cancer in treated areas. Moreover, vagotomy or local botulinum toxin type A administration enhances systemic chemotherapy efficacy and prolongs overall survival in patients with gastric cancer [25]. A phase II trial assessing endoscopic botulinum toxin injections into tumors and adjacent normal gastric tissue found that, in patients unsuitable for standard surgical resection, combining denervation with immunotherapy or targeted agents is a promising strategy. However, denervation aims to disrupt harmful nerve-tumor crosstalk within the lesion and its stroma; without precise targeting, harm may outweigh benefit, and some reports link denervation to accelerated onset and progression of gastric remnant carcinoma [255, 256]. Such findings highlight intratumoral delivery of neurotoxins as the most practical therapeutic approach. Still, chemical

denervation is inherently transient: over time, nerve fibers can reinnervate lesions, allowing tumor progression to recur [164].

Current clinical studies aim to optimize combination regimens. In patients with advanced digestive system cancers, pairing denervation therapies with immune checkpoint inhibitors may become a new research focus. Advances in neuroimaging techniques and biodegradable drug-delivery systems will enable denervation strategies with high spatial specificity and precise timing, reshaping the landscape of tumor neuromodulation therapies (Table 3).

Targeting neural signaling pathways

Targeting neuroendocrine factors

Targeting neuroendocrine factors such as NGF may cause fewer side effects than denervation therapies (Table 3), since preserving neural networks better supports antitumor immunity. Neurotrophins are essential for neuronal development under normal conditions, but once innervation is complete, they lose their trophic role and can instead trigger nociceptive signaling via specific receptors [257, 258]. NGF drives pathological axonogenesis within the TME [24, 166, 259], and NGF-neutralizing antibodies have become key inhibitors of intratumoral neural expansion [260, 261]. Systemic administration of these antibodies does not appear to impair cognitive function [257]. BDNF is also aberrantly expressed in multiple cancers, where it modulates tumor cell proliferation, invasion, and chemoresistance. Depending on prevailing signaling pathways and the microenvironment, BDNF may act as either a tumor suppressor or promoter [262–264]. Despite extensive preclinical efforts, BDNF-targeted therapies remain immature in clinical oncology. As a result, researchers are investigating miRNAs that directly regulate BDNF expression as potential cancer therapeutics [265]. The glial cell-derived neurotrophic factor (GDNF) signaling axis drives metastatic spread in breast cancer cells [266], and GDNF has been shown to enhance tumor progression [267]. Emerging studies of these and other neuroendocrine factors expand the therapeutic repertoire in cancer neuroscience.

In addition to classical neurotrophins, neuropeptides, which are distinct polypeptide neurotransmitters, play broad roles in both physiological and pathological contexts. Recent evidence indicates that the neuropeptide SP enhances tumor progression and drives metastatic dissemination [132, 268]. TME-localized NPU, a secreted neuropeptide, has emerged as a key mediator of crosstalk between malignant cells and their nonmalignant neighbors. NPU receptors appear on tumor cells and on immune, stromal, and endothelial populations within the TME. This distribution suggests that tumor-derived NPU engages these cell types through paracrine signaling, sculpting a niche that favors tumor expansion and invasion. However, the precise functions and molecular pathways by which NPU operates in the TME remain incompletely defined [82]. Neuropeptides released by nociceptors, such as CGRP, adrenomedullin (ADM), adrenomedullin 2 (ADM2), vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating peptide (PACAP), are increasingly recognized as key modulators of neuro-immune antitumor interactions [269]. To advance this research, chemical or genetic ablation of nociceptors is essential. Nociceptors engage diverse immune cell populations within the same tissue through distinct molecular pathways. Selective disruption of specific signaling modalities, for example by targeting individual neuropeptides, may be necessary to elicit effective antitumor responses. These findings suggest that interventions aimed at neuropeptides could offer innovative strategies in neuro-oncology.

Targeting neural receptors

β-adrenergic receptor blockers are routinely used to manage cardiovascular diseases. Emerging clinical evidence indicates that β-blocker therapy is associated with improved survival in cancer patients [270]. A study demonstrated that β-adrenergic receptor blockers improved survival rates in advanced non-small cell lung cancer patients with hypertension receiving radiotherapy [271]. In a national cohort of patients with HCC, researchers assessed the association between β-blocker prescriptions dispensed within 90 days prior to cancer diagnosis and liver cancer mortality as confirmed from a cause-of-death registry. After controlling for relevant confounders, results showed that during a median follow-up of 9.9 months, 1,601 patients died, among whom 1,309 died of liver cancer. Compared to non-users, the use of β-adrenergic receptor blockers [$n = 714$ (predominantly prior users, 93%)] was associated with a lower liver cancer mortality [0.82 (0.72–0.94); $p = 0.005$] [272]. Another study by this group also confirmed that β-blocker use was associated with improved bladder cancer-specific survival [273]. In a cohort of 3,561 patients with high-risk or metastatic prostate cancer, β-blocker therapy significantly reduced prostate cancer-specific mortality [274]. Furthermore, β-blockers act synergistically with cancer immunotherapies, enhancing antitumor efficacy [275]. Currently, there are limited studies on β-blockers improving digestive system tumors, with completed studies including tumor types such as non-small cell lung cancer and urinary tract tumors. Several clinical trials of β-adrenergic receptor inhibitors targeting various tumor types, including digestive system tumors, are currently underway. Whether β-blockers can improve survival in digestive system tumors and other cancers requires further research and validation. If findings are positive,

Table 3 Summary of therapeutic strategies targeting neural regulation in digestive system tumors

Methods	Typical example	Primary function	Mechanism of anti-tumor effects	Applicable tumor types	References/NCT numbers
Denervation					
Surgery or pharmacotherapy	Bilateral or unilateral truncal vagotomy; local injection of botulinum toxin type A (Phase II).	Disruption of innervation by surgery or drugs	The elimination of neural involvement in the promotion, progression, and metastasis of tumorigenesis.	Stomach cancer	NCT01822210
Targeting neural signaling pathways					
NGF inhibitors	NGF inhibitors (Preclinical)	Inhibition of NGF function	The role of NGF in promoting axon formation in the TME was prevented.	Pancreatic cancer; Melanoma	[166, 290–295]
BDNF inhibitors	BDNF inhibitors (Preclinical)	Inhibition of BDNF function	Blocking the effects of BDNF on the proliferation, invasion and drug resistance of tumor cells; blocking the ability of BDNF to act as a tumor promoter.	Gastric cancer; Colon adenocarcinoma	[291, 292]
GDNF inhibitors	GDNF inhibitors (Preclinical)	Inhibition of GDNF function	Blocking the role of GDNF in promoting tumor progression and metastasis.	Breast cancers	[293]
β-blocker	Carvedilol (Phase II; Clinical trials involving carvedilol included preoperative administration to prostate cancer patients until radical prostatectomy, and these studies have now been completed.); Propranolol (Early Phase I; Clinical trials investigating propranolol evaluated its therapeutic effects in patients with surgically unresectable locally recurrent or metastatic solid tumors. The findings demonstrate that propranolol may impede tumor growth by disrupting cancer cell utilization of hormones. This trial has now been completed).	Inhibition of β receptors function	Blocking the tumor-promoting effect of catecholamine neurotransmitters and increasing the survival rate of cancer patients; Synergetic with immunotherapy to promote anti-tumor efficacy.	Hepatocellular carcinoma; Melanoma; Breast cancer; Prostate cancer	NCT02013492; NCT02944201; [294, 295]
Trk receptors inhibitors	Larotrectinib (Phase I, Phase II, Phase I/II); Entrectinib (Phase I, Phase II); Selitrectinib (Phase I).	Inhibition of Trk receptors function	The same function as NGF inhibitors.	Colorectal cancer; Pancreatic cancer; Cholangiocarcinoma; Melanoma; Breast cancer; Non-small cell lung cancer	NCT02122913; NCT02637687; NCT02576431; NCT02568267; NCT03215511; [296, 297]
Anticholinergic drugs	Solifenacin (Phase III, Phase IV; Current clinical trials investigating solifenacin in tumor therapy primarily focus on symptomatic management of chemotherapy-induced adverse effects in prostate cancer, whereas clinical studies exploring its direct or indirect antitumor effects have not been initiated.)	Inhibition of cholinergic receptors function	Activating signaling cascades and classical cancer pathways to promote cancer progression; modulating stem cell functions to support tumor initiation.	Prostate cancer	NCT01777217; NCT02805452
Antipsychotics					

Table 3 (continued)

Methods	Typical example	Primary function	Mechanism of anti-tumor effects	Applicable tumor types	References/NCT numbers
Valproic acid	Valproic acid/Valproate (Phase I, Phase II; Clinical trials investigating valproate for cancer treatment encompass a broad spectrum of malignancies, ranging from digestive system tumor to thyroid carcinoma, non-Hodgkin lymphoma, and melanoma.)	Bipolar disorder Epilepsy; Migraine headaches;	Inhibits histone deacetylase to reduce cancer cell proliferation and induce apoptosis; induces differentiation and inhibits angiogenesis.	Digestive system tumor; Thyroid cancers; Non-Hodgkin's lymphoma; Melanoma.	NCT01552434; NCT01182285; NCT00109824; NCT02068586; [298, 299]
Phenothiazines	Chloropromazine (Phase I/II); Levomepromazine (Preclinical); Thioridazine (Phase I); Olanzapine (Preclinical); Pimozide (Preclinical).	Schizophrenia Psychosis; Antiemetic; Schizophrenia; Bipolar disorder; Tourette syndrome; Resistant tics.	Promotes cancer stem cell differentiation through dopamine receptor pathway; inhibits mitochondrial; DNA polymerase and decreases ATP production with selectively cytotoxicity and antiproliferative activity in leukemic cells.	Colon cancer; Pancreatic cancer; Acute myeloid leukemia.	NCT05433402; NCT02096289; [300]
Selective serotonin reuptake inhibitors (SSRI)	Citalopram (Preclinical); Fluoxetine (Early Phase I); Paroxetine (Preclinical); Sertraline (Preclinical).	Depression; Generalized anxiety disorder; Obsessive-compulsive disorder; Eating disorders; Stroke recovery; Premature ejaculation.	Reduces proliferation and induce apoptosis in cancer cells; down-regulates p-AKT to mediate the synergistic antiproliferative interaction with other chemo-drugs.	Colon cancer; Glioblastomas.	[301, 302]
Tricyclic antidepressants	Imipramine (Early Phase I); Trimipramine (Preclinical); Amitriptyline (Preclinical).	Major depression; Attention-deficit hyperactivity disorder; Insomnia; Chronic pain.	Inhibits cellular proliferation and induces cell apoptosis in different tumors including neuroendocrine tumors; improves the effectiveness of other chemotherapeutic agents.	Colon cancer; Breast cancer.	NCT03122444; [303]
MAO inhibitors	Selegiline (Phase II); Phenelzine (Phase I, Phase II); Tranylcypromine (Phase I).	Atypical depression; Panic disorder; Borderline personality disorder.	Inhibits BHC110/LSD1, as an important chromatin modification enzyme capable of demethylating histone.	Prostate cancer; Breast cancer; Lung cancer; Acute myeloid leukemia.	[304]
In combination with immunotherapy					
ICB and β-blocker	Propranolol and Pembrolizumab (Phase II); Tanezumab (Phase II, Phase III; Clinical trials for tumor treatment using Tanezumab alone are more common in palliative treatment for bone metastases, while clinical trials combining Tanezumab with neurosignal-blocking drugs such as β-blockers for tumor treatment have not yet been conducted).	ICB work by antagonizing checkpoint molecules (such as PD-1/PD-L1 and CTLA-4), thereby reversing tumor-mediated immune suppression and potentiating T cell-mediated tumor cytotoxicity.	β-blockers may enhance the therapeutic efficacy of immune checkpoint inhibitors.	Breast cancer; Melanoma.	NCT05741164; [286]

β-blockers have the potential to become valuable adjuvant therapies in digestive system tumors (Table 3).

Trk receptors are high-affinity binding sites for neurotrophins such as NGF and BDNF. In pancreatic cancer, inhibitors that block these ligand-receptor interactions effectively curb NGF-mediated cancer neurogenesis and prevent remodeling of the TME (Table 3) [21]. This approach also offers a novel strategy for precisely disrupting neuro-tumor interactions.

Combination therapy with antipsychotic drugs

Antipsychotic agents have emerged as potential chemotherapeutic candidates. Epidemiological data indicate that individuals with schizophrenia treated with these drugs experience a lower overall cancer incidence than the general population. Specifically, schizophrenia cohorts receiving antipsychotics have reduced prostate, colon, and rectal cancer rates, suggesting that these psychiatric medications may have antineoplastic properties [276–278]. In vitro and in vivo studies show that widely prescribed antipsychotics, including phenothiazines, olanzapine, pimozide, and valproic acid, induce apoptosis in multiple cancer cell lines [279–281]. Nevertheless, tricyclic antidepressants and selective serotonin reuptake inhibitors have shown inconsistent antitumor effects in preclinical models and retrospective oncology analyses. Although some of these agents have been tested in small prospective trials, definitive evaluation of their therapeutic benefit requires larger randomized controlled studies.

Electrical stimulation markedly contributes to brain tumor proliferation. It remains unknown whether electrical networks and complex neural circuits develop in peripheral tumors. To date, tumor microtubes mediating intercellular communication have been observed in pancreatic cancer, suggesting potential electrical processes outside the CNS. However, the mechanisms driving this phenomenon remain unclear. These insights have prompted research into the antitumor potential of antiepileptic drugs [282–284]. Although antiepileptic agents are routinely used to prevent seizures in patients with CNS tumors, they may also have ancillary anticancer effects by suppressing neuronal electrical activity. Similarly, analgesic compounds targeting sensory neurons have demonstrated antitumor efficacy in pancreatic cancer animal models [285]. Further investigation into its dual analgesic and anti-peripheral digestive system tumor properties may open new avenues in cancer neuroscience and offer fresh insights into the crosstalk between digestive system tumors and the nervous system. (Table 3).

Combined with immunotherapy

Recent clinical trials have shown that combining pembrolizumab with β-blockers may enhance the efficacy of pembrolizumab [286]. Building on this, a meta-analysis and retrospective study covering various ICB therapies found an association between β-blocker use and improved antitumor effects of ICB [287]. To elucidate the cellular mechanisms underlying this synergy, one study demonstrated that combining PRO with immunotherapies such as programmed death-ligand 1 (PD-L1) inhibitors prevents PD-L1 overexpression in ovarian cancer cells; the authors hypothesized that this combination strategy induces a more targeted response to PD-L1 inhibitors by suppressing endogenous PD-L1 expression in tumor cells [288]. These observations suggest that β-blockers may potentiate the efficacy of immune checkpoint therapies. Meanwhile, in animal models, combining β-blockers with immunotherapy extended overall survival (OS) in mice by enhancing immune cell activity, particularly the response to IL-2 [289]. Therefore, such combination immunotherapy strategies, inspired by cancer neuroscience, exhibit strong potential for clinical translation (Table 3).

This table broadly summarizes neuro-targeted cancer therapies, including denervation treatments, targeting neural signaling pathways, combined use of antipsychotic drugs, and combination immunotherapy. For each treatment modality, the table provides classic examples and the types of tumors treated, along with descriptions of their fundamental mechanisms and anti-tumor effects.

Limitations of the current research

Despite significant progress in recent years regarding the role of the neuro-immune axis in gastrointestinal tumorigenesis and progression, several limitations remain, primarily in the following aspects: (1) Most current studies rely on mouse xenograft or chemically-induced models, which significantly differ from humans in neural distribution, immune cell composition, and signaling pathways, limiting the clinical generalizability of findings. Additionally, traditional 2D co-culture systems and most organoid models lack endogenous neurons or immune cells, making it difficult to fully reproduce the spatial and functional complexities of the neuro-immune-tumor interactions [305]. (2) Current research predominantly relies on endpoint sampling, which fails to dynamically capture the transient associations between neurotransmitter release and immune cell responses across multiple spatial-temporal scales, resulting in insufficient temporal resolution. Even with electrophysiological techniques or high-resolution imaging applied in mice, limitations in signal-to-noise ratio, imaging depth, and labeling probe kinetics hinder the synchronized real-time monitoring of neural and immune signals within the TME. (3) Neuro-targeted drugs (e.g., β-blockers, NGF inhibitors) exhibit significant efficacy variability in retrospective clinical samples and are frequently associated with systemic side effects, such as cardiovascular issues. The substantial

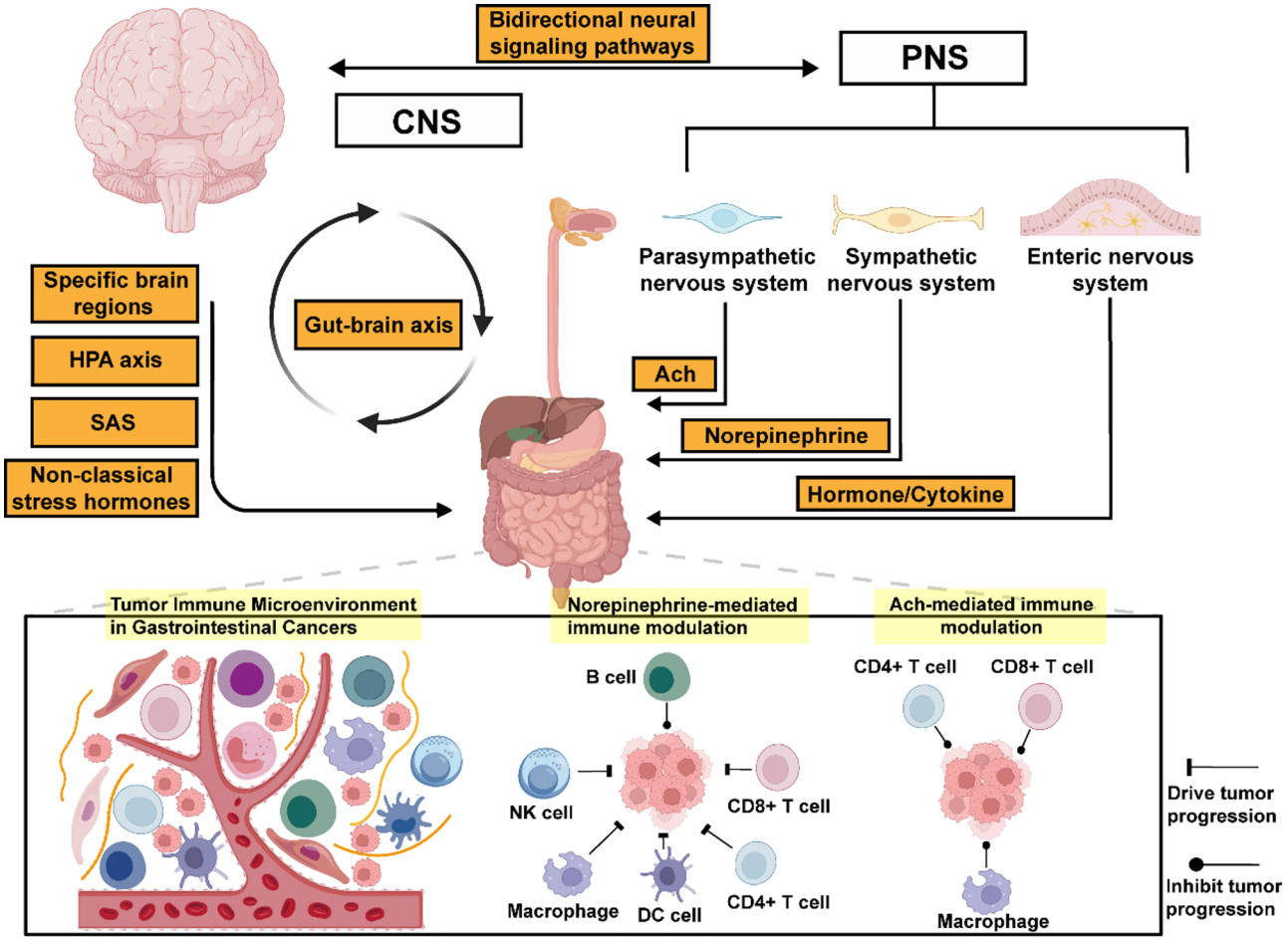

Fig. 6 Neuro-immune-digestive system tumor interaction network. Schematic diagram illustrating the interactions among the CNS, PNS, ENS, immune cells, and tumor cells, and this complex neuro-immune-tumor regulatory network lays the groundwork for neuro-immune-tumor discipline

heterogeneity among patients in terms of nerve fiber density, immune infiltration types, and molecular phenotypes has yet to yield reliable biomarkers predictive of therapeutic efficacy, significantly increasing the challenges for clinical translation. (4) Although recent studies have employed single-cell transcriptomics, spatial omics, and metabolomics, current approaches remain inadequate in terms of multi-omics data standardization, cross-platform integration, and dynamic modeling [306]. Furthermore, existing bioinformatics tools have not yet developed comprehensive models capable of simultaneously capturing neural signaling, immune cell lineage evolution, and metabolic reprogramming information. These limitations in multi-omics data integration and bioinformatics analysis constrain the accurate depiction of neuro-immune-tumor interactions. Significant efforts remain necessary to advance neuro-immune research in gastrointestinal tumors from mechanistic understanding towards precision intervention and clinical application.

Conclusions

Nerve-immune-tumor interactions in digestive-system cancers form a highly dynamic regulatory network. At the local level, tumor cells and nearby nerves engage in bidirectional secretion of neurotransmitters and neurotrophic factors. This crosstalk drives directed ingrowth of nerve fibers and supports tumor proliferation. At the systemic level, the central nervous system regulates global immune surveillance through descending neural pathways and the HPA axis. Chronic stress then reshapes antitumor immunity via neuroendocrine signals. Integrated analyses reveal that tumor cells co-opt receptors and effectors shared by neural and immune pathways. This sharing establishes a distinct "neuro-immune niche" within the TME. Such a niche provides a conceptual basis for therapies that simultaneously target neural signals and immune checkpoints (Figure 6).

Looking ahead, researchers should employ single-cell omics and high-resolution imaging to map the spatial and temporal patterns of nerve-fiber infiltration, nerve-immune-cell contacts, and nerve-tumor-cell interfaces

across different digestive cancers. Clarifying how other neurotransmitter families affect tumor immunomodulation will guide the design of dosing regimens, treatment sequences, and combination approaches that pair neuroregulatory agents with immune checkpoint blockers in clinical trials. Advancing neuro-immune-tumor co-intervention also requires detailed knowledge of tissue distribution, blood-brain barrier penetration, and potential neurotoxic or cardiovascular side effects of neural-targeting small molecules and antibodies. Finally, identifying reliable neural biomarkers will be essential for translating these strategies into clinical practice.

In summary, integrating cancer neuroscience with tumor immunology offers new opportunities for precision therapy in digestive-system cancers. Multidisciplinary collaboration, technological innovation, and rigorous clinical validation are essential to enhance patient response rates and improve long-term survival.

Abbreviations

NGF	Nerve growth factor
HPA	Hypothalamic-pituitary-adrenal
PDAC	Pancreatic ductal adenocarcinoma
NT-3/4	Neurotrophin-3/4
BDNF	Brain-derived neurotrophic factor
INS-GAS	Insulin-gastrin
ENS	Enteric nervous system
CRC	Colorectal cancer
SCs	Schwann cells
PNI	Perineural invasion
TNM	Tumor-node-metastasis
EGCs	Enteric glial cells
HCC	Hepatocellular carcinoma
TH	Tyrosine hydroxylase
VAChT	Vesicular acetylcholine transporter
TrkA	Tropomyosin receptor kinase A
SMP	Submucosal plexus
CM	Circular muscle
MP	Myenteric plexus
LM	Longitudinal muscle
TME	Tumor microenvironment
NPU	Neuropeptide U
CNS	Central nervous system
SCN	Suprachiasmatic nucleus
GABA	γ-aminobutyric acid
TNF	Tumor necrosis factor
IFN-γ	Interferon-γ
ARC	Arcuate nucleus
PVN	Paraventricular nucleus
VMN	Ventromedial hypothalamus
DMH	Dorsomedial hypothalamus
OX1R	Orexin receptor type 1
EE	Environmental enrichment
GC	Glucocorticoid
GR	Glucocorticoid receptor
MAPK	Mitogen-activated protein kinase
CDK1	Cyclin-dependent kinase 1
EMT	Epithelial-mesenchymal transition
TGF-β	Transforming growth factor-β
SOX-2	SRY-box transcription factor 2
MDSC	Myeloid-derived suppressor cell
LCK	Lymphocyte-specific protein tyrosine kinase
FYN	FYN proto-oncogene, Src family tyrosine kinase
TCR	T cell receptor
ERK	Extracellular signal-regulated kinase
DRD2	Dopamine receptor D2
cAMP	Cyclic adenosine monophosphate
VEGF	Vascular endothelial growth factor
SAS	Sympatho-adrenal system
CCR	C-C motif chemokine receptor
CCL	C-C motif chemokine ligand
NK	Natural killer
ANS	Autonomic nervous system
VLM	Ventrolateral medulla
PNS	Peripheral nervous system
β_2-AR	β_2-adrenergic receptor
CREB	cAMP response element-binding protein
NF-κB	Nuclear factor kappa B
ACh	Acetylcholine
nAChRs	Nicotinic acetylcholine receptors
mAChRs	Muscarinic acetylcholine receptors
CHRM3	Cholinergic receptor muscarinic 3
EGFR	Epidermal growth factor receptor
YAP	Yes-associated protein
ChAT	Choline acetyltransferase
CGRP	Calcitonin gene-related peptide
CSCs	Cancer stem cells
M3R	Muscarinic M3 receptor
PD-1	Programmed cell death protein 1
ICB	Immune checkpoint blockade
TFF2	Trefoil factor family 2
CXCR4	C-X-C chemokine receptor type 4
RAMP3	Receptor activity-modifying protein 3
CALARL	Calcitonin receptor-like receptor
Th1	T helper 1 cell
Th2	T helper 2 cell
ATF3	Activating transcription factor 3
ISO	Isoproterenol
PDX	Patient-derived xenograft
DSS	Dextran sulfate sodium
VNS	Vagus nerve stimulation
DCs	Dendritic cells
MPO	Myeloperoxidase
CAFs	Cancer-associated fibroblasts
PanIN	Pancreatic intraepithelial neoplasia
PI3K	Phosphatidylinositol-3-kinase
AKT	Protein kinase B
mTOR	Mammalian target of rapamycin
NTRK1	Neurotrophin receptor kinase 1
DNA	Deoxyribonucleic acid
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CCND1	Cyclin D1
HIF	Hypoxia-inducible factor
GAD67	Glutamate decarboxylase 67
PKA	Protein kinase A
ICER	Inducible cAMP early repressor
NLGN3	Neuroligin-3
ADAM10	A disintegrin and metalloproteinase 10
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
GDNF	Glial cell-derived neurotrophic factor
SP	Substance P
ADM	Adrenomedullin
VIP	Vasoactive intestinal peptide
PACAP	Pituitary adenylate cyclase-activating peptide
PRO	Propranolol
PD-L1	Programmed death-ligand 1
OS	Overall survival
RAS/Ras	Rat sarcoma viral oncogene homolog
JNK	c-Jun N-terminal kinase
MMP-2	Matrix metalloproteinase-2
MMP-9	Matrix metalloproteinase-9
COX-2	Cyclooxygenase-2
γ-H2AX	Phosphorylated histone H2AX
MYC	Myelocytomatosis oncogene
AMPK	AMP-activated protein kinase
SSRI	Selective serotonin reuptake inhibitors
MAO	Monoamine oxidase
Treg	Regulatory T cell

Th17	T helper 17 cell
HDACs	Histone deacetylases
FFAR2	Free fatty acid receptor 2
ASF	Altered Schaedler flora

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Author contributions
ZY Jiao, WL Jin, HN Sun and XY Jiang conceptualized and designed the study; HN Sun, T Wang and MD Li drafted the manuscript and compiled the related literature; XE He and Y Ma designed the figures/tables and summarized the content; HN Sun, MD Li and T Wang prepared the graphical materials; XK li, HN Sun, T Wang and XY Jiang reviewed and revised the manuscript. All authors have read and agreed to the submitted version of the manuscript.

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