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The neuro-immune axis in cancer: from mechanisms to therapeutic opportunities

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Abstract

In recent years, neural mechanisms involved in tumor initiation, progression, and immune regulation have garnered growing attention, fueling the rapid advancement of the burgeoning interdisciplinary domain of neuro-oncology. As a central component of physiological homeostasis, the neurophysiological system also exerts significant influence on the development and dynamics of the tumor microenvironment via complex neuro-immune signaling. Studies have shown that neurotransmitters, neuropeptides, and their mediated signaling pathways can directly or indirectly affect the functional state of tumor-associated immune cells, notably B cells, T cells, macrophages, myeloid-derived suppressor cells, and dendritic cells, thereby contributing to tumor immune evasion. This review systematically summarizes recent advances in neuroimmune interactions within the tumor microenvironment, highlighting the therapeutic potential of neural targets such as β-adrenergic and acetylcholine receptors. It also evaluates the repurposing potential of existing neuroactive drugs in cancer immunotherapy and their future application prospects. Although research in this field is still in its early stages, a deeper understanding of neuro-immune interaction mechanisms is expected to provide new ideas and theoretical foundations for innovative cancer treatment strategies.

Keywords Cancer neuroscience, Tumor immune microenvironment, Neuro-immune interaction, Immune evasion, Tumor immunotherapy

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Introduction

In recent years, the pivotal function of the tumor microenvironment (TME) in tumor initiation, progression, and therapeutic response has been widely recognized [1, 2]. The TME is composed of tumor cells, fibroblasts, immune cells, the extracellular matrix, vascular endothelial cells, and signaling molecules, forming a highly dynamic and complex ecosystem [3, 4]. Traditional oncological investigations have primarily centered around the interaction between tumors and host immunity, particularly enhancing T cell responses through checkpoint blockade therapies, which have driven major breakthroughs in cancer immunotherapy [5, 6]. However, growing evidence from recent research suggests that the nervous system, serving as a key element within the TME, also exerts a critical function in regulating immune responses and tumor biology [7]. The nervous system supports tumor survival and releases neurochemical mediators like neurotransmitters, neuropeptides, and hormones that regulate the activity of key immune subsets, including T cells, macrophages, myeloid-derived suppressor cells (MDSCs), and dendritic cells, ultimately affecting tumor progression and response to therapy [8–12]. The central nervous system (CNS), consisting of the brain and spinal cord, is responsible for the integration of neural signals and higher-order regulation. The peripheral nervous system (PNS), composed of motor nerves, sensory nerves, and autonomic nerves (sympathetic and parasympathetic), mediates signal transmission between the CNS and peripheral tissues. The sympathetic nervous system primarily mediates the "stress—fight or flight" response, with its postganglionic fibers releasing norepinephrine (NE) as the main neurotransmitter, while epinephrine (Epi), secreted by the adrenal medulla, acts as a hormone in the bloodstream. The parasympathetic nervous system mainly mediates the "rest and digest" response, with acetylcholine (ACh) as its neurotransmitter. The somatic nervous system not only controls skeletal muscle movement but also contains certain sensory fibers, such as nociceptors, which can participate in immune regulation. The multi-level and multi-pathway characteristics of the nervous system provide a biological basis for the complex interactions between the nervous and immune systems within the tumor microenvironment. Neurotransmitters and neuropeptides can modulate immune cell functions, thereby influencing the immune status and progression of tumors. The nervous system may intervene in tumor-related immune regulation through three major mechanisms:

1. Direct local neural input regulation: Nerve fibers (such as sensory, sympathetic, or parasympathetic nerves) are capable of secreting neurotransmitters and neuropeptides such as NE, ACh, substance P, and brain-derived neurotrophic factor—within the local microenvironment, directly acting on immune cells in the TME [13] (Fig. 1A; Tables 1 and 2).
2. CNS neurotransmitter-mediated peripheral immune regulation: Although neural signaling molecules including dopamine (DA), gamma-aminobutyric acid (GABA), 5-hydroxytryptamine (5-HT), and glutamic acid (Glu) have traditionally been considered to function primarily within the CNS, research indicates that under pathological or stress conditions, these molecules can be synthesized and released in peripheral tissues, or enter the tumor microenvironment via the bloodstream, where they act on immune cells to modulate their function and immune responses [14] (Fig. 1B; Tables 1 and 2).
3. Hormone-mediated systemic immune modulation: The nervous system can activate endocrine glands (such as the ovaries, testes, pancreas, and thyroid) to secrete hormones that circulate through the bloodstream to peripheral organs like the lungs, liver, and intestines, thereby systemically modulating immune cell function [15, 16] (Fig. 1C; Tables 1 and 2).

This emerging field, known as cancer neuroscience, is gradually uncovering the complex interaction network among tumors, the immune system, and the nervous system. It not only provides a new theoretical framework for understanding tumor development but also offers novel perspectives and potential targets for precise TME modulation and enhancement of immunotherapy efficacy. Given these considerations, this article provides a comprehensive overview of how both the central and PNS modulate immune regulation in peripheral tumor. It focuses on elucidating the molecular mechanisms of neuro-immune interactions, assessing the therapeutic potential of existing neuromodulatory drugs in anti-tumor treatment, and exploring future directions for their synergistic application with immunotherapy strategies.

Direct local neural input regulation

Sympathetic nervous system

The sympathetic nervous system influences the development, distribution, and functional state of immune cells in peripheral immune organs (like the lymph nodes, bone marrow, and spleen) through the release of catecholamine neurotransmitters, including NE and epinephrine (E), particularly under stress conditions (Fig. 2A). Studies have shown that sympathetic nerve terminals are widely distributed in T cell-rich regions of the spleen and lymph nodes, where they regulate T cell expansion

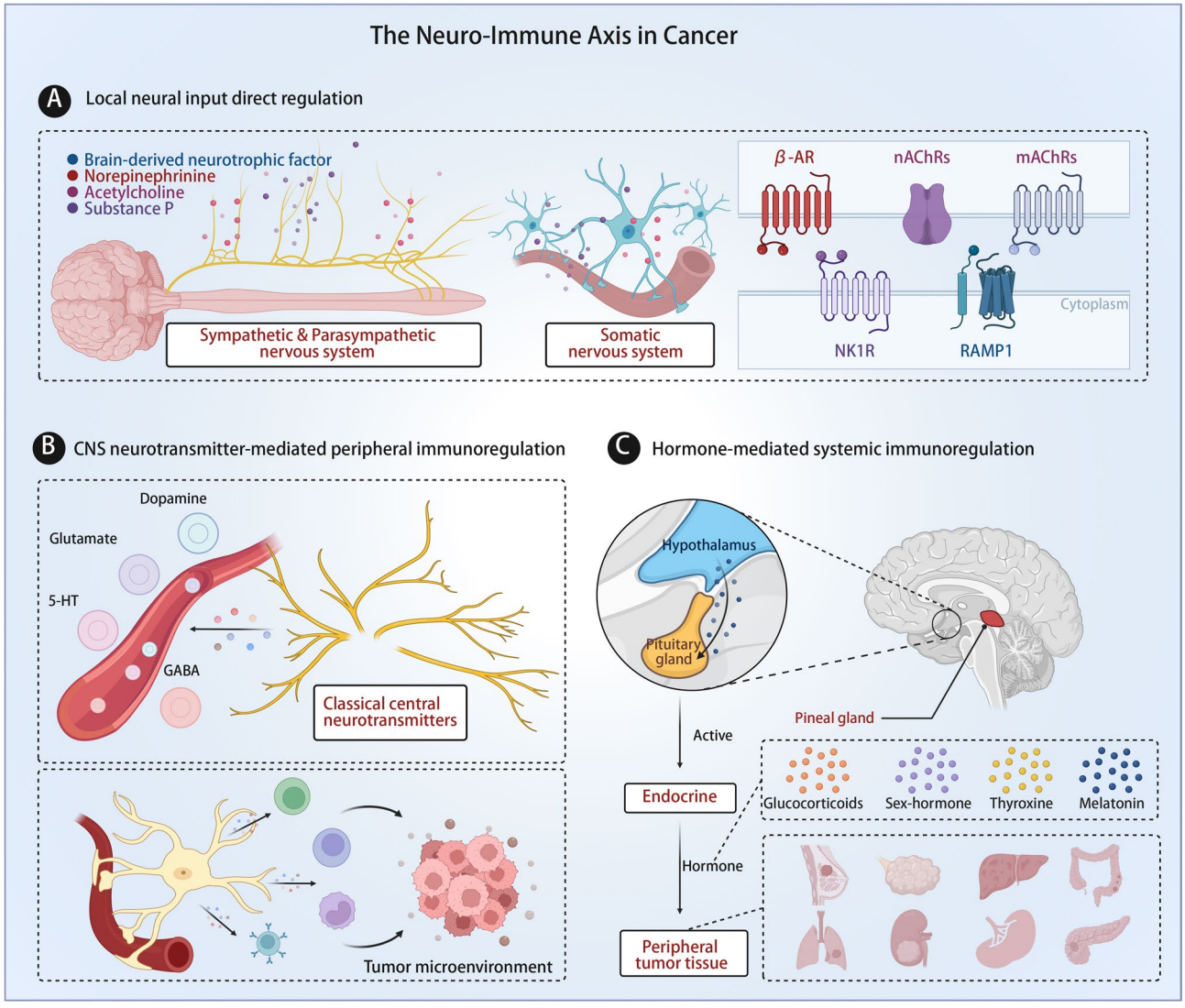


Fig. 1 Regulatory mechanisms of the neuro-immune axis in tumors. The nervous system participates in tumor-related immune regulation through three main pathways: (**A**) Direct regulation by local neural input: Sensory, sympathetic, and parasympathetic nerve fibers can release neurotransmitters and neuropeptides such as norepinephrine, ACh, substance P, and brain-derived neurotrophic factor (BDNF) within the tumor microenvironment, directly influencing the function of immune cells in the TME. (**B**) Peripheral immune regulation mediated by central neurotransmitters: Neurotransmitters such as dopamine, serotonin (5-hydroxytryptamine, 5-HT), γ-aminobutyric acid (GABA), and glutamate can be synthesized and released in peripheral tissues or enter the tumor microenvironment (TME) via blood circulation, acting on immune cells to modulate their activity. (**C**) Hormone-mediated systemic immune regulation: The nervous system can activate endocrine glands (such as the thyroid, pancreas, ovaries, and testes) to secrete hormones. These hormones act on peripheral tissues such as the lungs, liver, and intestines, thereby systemically regulating immune cell function

and cytokine secretion by activating β-adrenergic receptors (β-ARs) [17–20] (Fig. 2B). Stress responses enhance sympathetic activity, leading to upregulation of pro-inflammatory cytokines (e.g., IL-1β, IL-6, GRO1) in the spleen, while splenic denervation significantly suppresses their expression [128–131]. In addition, the sympathetic nervous system also influences the immune status of the TME by modulating dendritic cell (DC) function and, in turn, affecting T cell responses. In mouse models, researchers compared immune states under standard temperature (ST, 22 °C) and thermoneutral temperature (TT, 30 °C). The ST condition simulates chronic cold stress and sustained sympathetic activation, while TT alleviates such stress. Without tumors, no significant variations were observed in the composition of immune cells in the spleen across groups. However, following tumor inoculation, ST mice exhibited a significant increase in splenocyte numbers, accelerated tumor growth, and higher proportions of $CD11b^+$ myeloid cells and $B220^+CD11c^+$ plasmacytoid DCs compared to the TT group [21] (Fig. 2C). Further research found that TT conditions reduced the levels of MDSCs, enhanced $CD8^+$ T cell activation, and decreased immunosuppressive cells such as Tregs and MDSCs, indicating that stress

Table 1 Neurotransmitters and pituitary-regulated peripheral hormones regulating immune cells and the tumor microenvironment

Signal type	Source	Immune cell affected	Effect	Cancer context	References
Autonomic neurotransmitter	Norepinephrine	T cells	Anti-inflammatory	No	[17–20]
Autonomic neurotransmitter	Norepinephrine	Dendritic cells	Anti-inflammatory	Yes	[21]
Autonomic neurotransmitter	Norepinephrine	MDSCs	Anti-inflammatory	Yes	[22–29]
Autonomic neurotransmitter	Norepinephrine	T cells	Anti-inflammatory	Yes	[22]
Autonomic neurotransmitter	Norepinephrine	NK cells	Anti-inflammatory	Yes	[30–32]
Autonomic neurotransmitter	Norepinephrine	Th1	Anti-inflammatory	Yes	[30, 31]
Autonomic neurotransmitter	Norepinephrine	CD4$^+$ T cells, B cells	Acute stress: pro-inflammatory	No	[33, 34]
Autonomic neurotransmitter	Norepinephrine	CD4$^+$ T cells, B cells	Chronic stress: anti-inflammatory	No	[33, 34]
Autonomic neurotransmitter	Norepinephrine	Pancreatic cancer cells	Pro-tumoral	Yes	[35]
Autonomic neurotransmitter	Norepinephrine	Macrophages	Pro-tumoral	Yes	[36–42]
Autonomic neurotransmitter	Norepinephrine	Tregs	Anti-inflammatory	No	[43]
Autonomic neurotransmitter	Norepinephrine	CD8$^+$ T cells	Pro-tumoral	Yes	[44, 45]
Autonomic neurotransmitter	Acetylcholine	Macrophages	Anti-inflammatory	No	[46]
Autonomic neurotransmitter	Acetylcholine	T cells	Anti-tumoral	Yes	[47]
Autonomic neurotransmitter	Acetylcholine	TAMs	Pro-inflammatory	Yes	[48, 49]
Autonomic neurotransmitter	Acetylcholine	MDSCs	Anti-inflammatory	No	[50]
Autonomic neurotransmitter	Acetylcholine	CD8$^+$ T cells	Anti-inflammatory	Yes	[51]
Autonomic neurotransmitter	Acetylcholine	NK cells	Anti-inflammatory	No	[52, 53]
Autonomic neurotransmitter	Acetylcholine	Tumor-associated epithelial cells	Anti-tumoral	Yes	[54, 55]
Autonomic neurotransmitter	Acetylcholine	Treg	Anti-inflammatory	No	[56]
Sensory neurotransmitter	Substance P	T cells	Pro-inflammatory	No	[57–59]
Sensory neurotransmitter	Substance P	Macrophages	Pro-inflammatory	No	[57–59]
Sensory neurotransmitter	Substance P	Neutrophils	Pro-inflammatory	No	[57–59]
Sensory neurotransmitter	CGRP	CD8$^+$ T cells	Anti-inflammatory	Yes	[60]
Sensory neurotransmitter	CGRP	Macrophages, DC cells	Anti-inflammatory	No	[61]
Sensory neurotransmitter	CGRP	Eosinophils, T cells	Pro-inflammatory	No	[62, 63]
CNS neurotransmitter	Glutamate	Dendritic cells	Anti-inflammatory	Yes	[64]
CNS neurotransmitter	Glutamate	Th17	Anti-inflammatory	No	[65]
CNS neurotransmitter	Glutamate	Myeloid cells	Anti-tumoral	Yes	[66]
CNS neurotransmitter	Glutamate	CD8$^+$ T cells	Pro-inflammatory	Yes	[67]
CNS neurotransmitter	Glutamate	NK cells	Pro-inflammatory	Yes	[67]
CNS neurotransmitter	Glutamate	Macrophages	Anti-inflammatory	No	[68–70]
CNS neurotransmitter	Glutamate	MDSCs	Pro-tumoral	Yes	[71]
CNS neurotransmitter	Glutamate	Macrophages	Pro-inflammatory	No	[72]
CNS neurotransmitter	Glutamate	T cells	Pro-inflammatory	No	[73–75]
CNS neurotransmitter	Glutamate	T cells	Anti-inflammatory	No	[76]
CNS neurotransmitter	Serotonin	Tumor cells	Pro-tumoral	Yes	[77]
CNS neurotransmitter	Serotonin	T cells	Anti-inflammatory	Yes	[78]
CNS neurotransmitter	Serotonin	CD8$^+$ T cells	Pro-inflammatory	Yes	[79]
CNS neurotransmitter	Serotonin	Macrophages	Anti-inflammatory	No	[80, 81]
CNS neurotransmitter	Serotonin	Dendritic cells	Anti-inflammatory	No	[82–84]
CNS neurotransmitter	Serotonin	Neutrophils, Monocytes	Anti-inflammatory	No	[85]
CNS neurotransmitter	Serotonin	Hepatic stellate cells	Pro-tumoral	Yes	[86]
CNS neurotransmitter	Dopamine	T cells	Anti-inflammatory	Yes	[87]
CNS neurotransmitter	Dopamine	Tumor cells	Pro-inflammatory	Yes	[88]
CNS neurotransmitter	Dopamine	T cells	Pro-inflammatory	Yes	[88]
CNS neurotransmitter	Dopamine	TAMs	Pro-inflammatory	Yes	[89–91]
CNS neurotransmitter	Dopamine	MDSCs	Anti-tumoral	Yes	[92]
CNS neurotransmitter	Dopamine	NK cells	Pro-inflammatory	No	[93]
CNS neurotransmitter	GABA	TAM	Anti-inflammatory	Yes	[94]
CNS neurotransmitter	GABA	Dendritic cells	Anti-inflammatory	Yes	[95]
CNS neurotransmitter	GABA	CD8$^+$ T cells	Anti-inflammatory	No	[96]
Hormone	Glucocorticoids	DCs	Pro-inflammatory	No	[97, 98]

Table 1 (continued)

Signal type	Source	Immune cell affected	Effect	Cancer context	References
Hormone	Glucocorticoids	T cells	Anti-inflammatory	No	[99–102]
Hormone	Glucocorticoids	T cells	Anti-inflammatory	Yes	[103]
Hormone	Glucocorticoids	TAMs	Anti-inflammatory	Yes	[104]
Hormone	Glucocorticoids	MDSCs	Anti-inflammatory	Yes	[105]
Hormone	Glucocorticoids	NK cells	Anti-inflammatory	No	[106]
Hormone	Glucocorticoids	Neutrophils	Anti-inflammatory	No	[107–110]
Hormone	Androgens	$CD8^+$ T cells	Anti-inflammatory	Yes	[111–113]
Hormone	Estrogens	Tumor cells (NSCLC)	Anti-inflammatory	Yes	[114]
Hormone	Estrogens	TAMs	Anti-inflammatory	Yes	[115, 116]
Hormone	Estrogens	T cells	Anti-inflammatory	Yes	[117, 118]
Hormone	Estrogens	MDSCs	Anti-inflammatory	Yes	[119]
Hormone	Thyroid Hormones	$CD8^+$ T cells	Anti-inflammatory	Yes	[120]
Hormone	Thyroid Hormones	Cancer cells	Pro-tumoral	Yes	[121]
Hormone	Melatonin	NK cells	Pro-inflammatory	Yes	[122]
Hormone	Melatonin	Neutrophils	Anti-inflammatory	Yes	[123]
Hormone	Melatonin	Tumor cells (NSCLC)	Pro-inflammatory	Yes	[124]
Hormone	Melatonin	Tumor cells (HNSCC)	Anti-tumoral	Yes	[125]
Hormone	Melatonin	Tumor cells (HCC)	Anti-tumoral	Yes	[126]
Hormone	Melatonin	Tumor cells (GC)	Pro-inflammatory	Yes	[127]
Hormone	Melatonin	Macrophages	Pro-inflammatory	Yes	[127]

alleviation can reshape antitumor immunity [22]. Consistently, breast cancer patients with elevated stress levels also showed increased MDSCs proportions in their tumors [23]. Postoperative stress, another common form of stress, has been shown to promote immune suppression. Several studies have associated high postoperative stress with increased tumor recurrence, suggesting that sympathetic activation weakens immune surveillance and facilitates tumor metastasis [132]. For example, in a rat model of post-mastectomy breast cancer, sympathetic activation reduced natural killer (NK) cell cytotoxicity, which could be reversed by the β-AR blocker propranolol [30]. Similarly, in melanoma models, stress-induced elevation of NE suppressed IFN-γ secretion by Th1 cells, impaired NK cell function, and accelerated tumor progression [30, 31] (Fig. 2D). Moreover, acute stress can enhance IgG1 and interferon production by activating adrenergic receptors on $CD4^+$ T cells and B cells, whereas chronic stress induces their apoptosis, demonstrating a dual effect of stress on immune regulation depending on its nature [33, 34] (Fig. 2E). Overall, stress activates the sympathetic-adrenal signaling axis, promoting the accumulation of immunosuppressive cells such as MDSCs and Tregs in the TME, while impairing the function of effector immune cells like $CD8^+$ T cells and NK cells.

At the molecular level, NE primarily mediates immunosuppressive effects through the β2-AR expressed on various immune cells [133]. In pancreatic cancer cells, norepinephrine stimulation downregulates MHC-I and costimulatory molecule B7-1 while upregulating immunosuppressive molecules such as indoleamine 2,3-dioxygenase (IDO) and PD-L1, helping tumor cells evade immune recognition [35] (Fig. 2F). β-AR signaling promotes the secretion of immunomodulatory factors such as IL-6 and IL-8 by tumor and myeloid cells and induces macrophage reprogramming toward an immunosuppressive phenotype characterized by IL-6, TGF-β, VEGF, MMPs, and COX-2 secretion [36–42] (Fig. 2G). Meanwhile, tumor-derived GM-CSF induces MDSCs to express β2-AR, forming a positive feedback loop and enhancing their suppressive capacity through fatty acid oxidation (FAO), with CPT1A playing a key role [24–26]. Treatment with the β-AR agonist isoproterenol (ISO) further enhances MDSC immunosuppressive properties by upregulating Arginase-I and PD-L1, which suppress T cell function through L-arginine depletion and immune checkpoint pathways, respectively [27–29] (Fig. 2H). In Tregs, NE promotes CTLA-4 and IL-10 expression, further inhibiting effector T cell responses [43] (Fig. 2I). In $CD8^+$ T cells, NE induces PD-1 expression, suppresses IL-2 and IFN-γ production, and impairs antitumor function [43, 134, 135] (Fig. 2J). In B cell lymphoma models, ISO suppresses $CD8^+$ T cell proliferation and IFN-γ expression via β-AR signaling in the hematopoietic system, reducing responses to PD-1/4-1BB immunotherapy and significantly lowering tumor-free survival rates

Table 2 Overview of neural receptors involved in tumor immune regulation

Receptor (Ligand)	Immune cells affected	Model (Human/Mouse)	Tissue niche	Cancer relevance	References
β2-AR (NE)	PDAC cells	Human	TME	Tumor cells evade immune recognition	[35]
β2-AR (NE)	Macrophages	Human/Mouse	TME	Promotes tumor immunosuppressive phenotype	[36–42]
β2-AR (NE)	MDSC	Human/Mouse	TME	Promotes tumor immunosuppressive phenotype	[24–29]
β2-AR (NE)	$CD8^+$ T cells	Mouse	TME	Suppresses antitumor effects	[44, 45]
nAChRs (ACh)	T cells	Mouse	TME	Inhibits colorectal cancer	[47]
nAChRs (ACh)	TAM	Human/Mouse	TME	Attenuates inflammatory signaling	[48, 49]
mAChRs (ACh)	Tumor-associated epithelial cells ($CD44^+$)	Human/Mouse	TME	Inhibits tumor growth	[54, 55]
M3R (ACh)	$CD8^+$ T cells	Human	TME	Anti-inflammatory	[51]
CGRPR (CGRP)	$CD8^+$ T cells	Human/Mouse	TME	Anti-inflammatory	[60]
mGluR4 (Glutamate)	Dendritic cells	Mouse	TME	Anti-inflammatory	[64]
mGluR4 (Glutamate)	Myeloid cells	Human/Mouse	TME	Suppressing tumor progression	[66]
mGluR4 (Glutamate)	$CD8^+$ T cells	Human/Mouse	TME	Promotes cytotoxic activity	[67]
mGluR4 (Glutamate)	NK cells	Human/Mouse	TME	Promotes cytotoxic activity	[67]
mGluR2/3 (Glutamate)	MDSCs	Mouse	TME	Promotes tumor growth	[71]
5-HTR5A/7 (Serotonin)	T cells	Human	TME	Suppresses cytotoxic T lymphocytes	[78]
D1R (Dopamine)	T cells	Human	TME	Inhibits T cell proliferation and cytotoxicity	[87]
D2R (Dopamine)	Tumor cells	Human/Mouse	TME	Decreases PD-L1 expression	[88]
D2R (Dopamine)	T cells	Human/Mouse	TME	Decreases PD-1 on T cells	[88]
D4R (Dopamine)	TAMs	Human/Mouse	TME	Decreases PD-1 on T cells	[89–91]
D1R (Dopamine)	MDSCs	Human/Mouse	TME	Enhancing anti-tumor immunity	[92]
GABA_B (GABA)	Dendritic cells	Human/Mouse	TME	Blocks the recruitment of dendritic cells	[95]

[44] (Fig. 2K). Additionally, β-AR signaling inhibits type I and type II interferon production, further weakening antitumor immunity [45]. NE also impairs NK cell cytotoxicity by downregulating key effector molecules such as perforin and granzyme [32] (Fig. 2L). In summary, NE promotes the establishment of an immunosuppressive environment through β2-AR-mediated regulation of immune cell function, thereby impairing antitumor immune responses [42, 136].

Targeting β-AR signaling has shown immune-enhancing potential in various models. In HPV-related tumor models, propranolol combined with STxBE7 vaccine and IFNα significantly increased $CD8^+$ T cell infiltration. Although T cell function was not directly enhanced, the effect was prominent during the initial activation stage, likely due to high β2-AR expression in lymph node T cells [40]. In melanoma and fibrosarcoma models, propranolol combined with anti-PD-1 antibody and IL-2 treatment increased T cell infiltration, reduced MDSCs density, and enhanced PD-L1 expression in tumor-associated macrophages (TAMs), improving immunotherapy efficacy [137]. Propranolol also alleviated T cell exhaustion by reducing the expression of PD-1, FOXP3, and LAG3, boosting cytotoxicity, and enhancing glucose uptake and

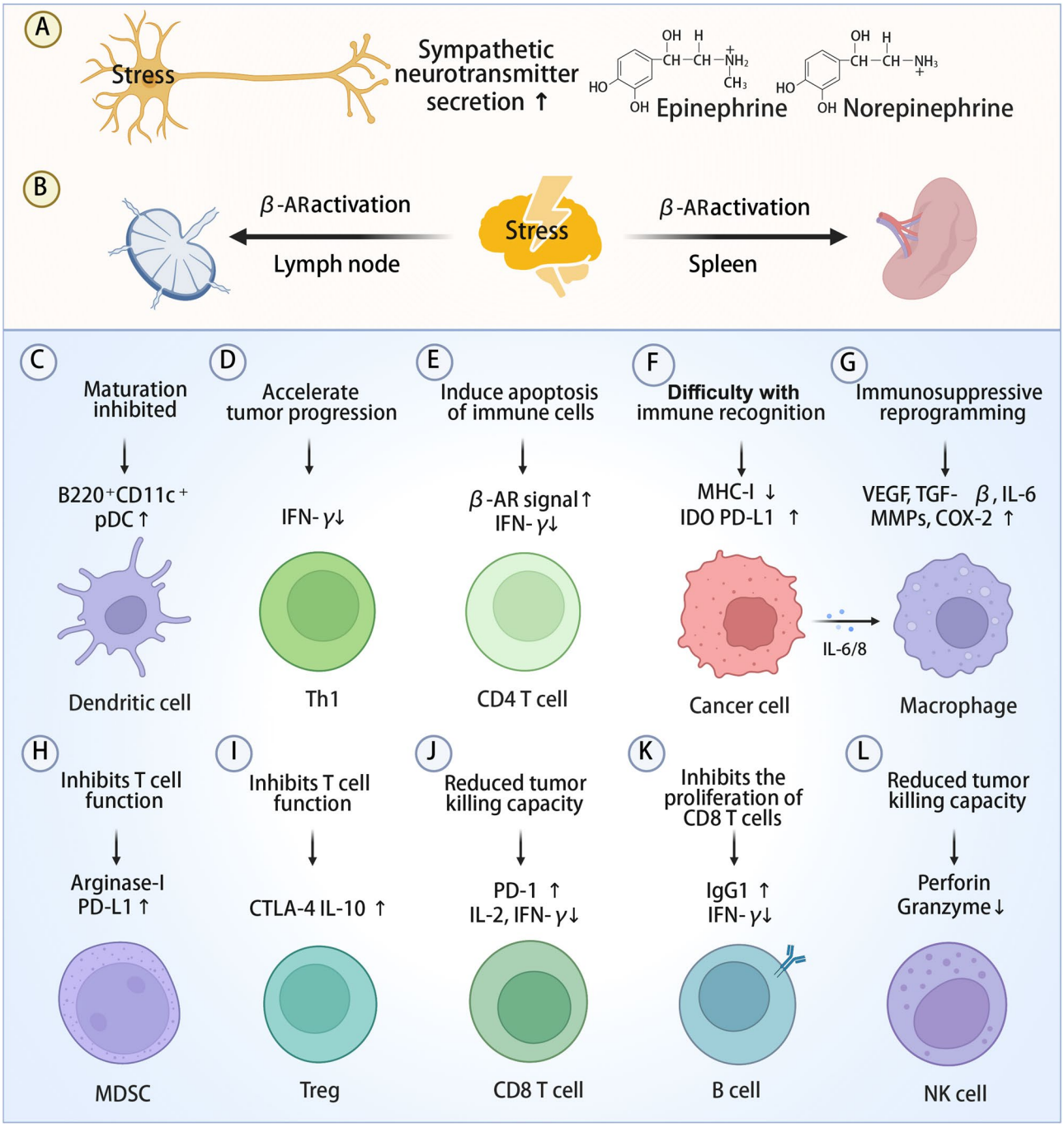


Fig. 2 Stress-induced sympathetic nervous system regulation of the tumor immune microenvironment. (**A**) under stress, catecholamines such as norepinephrine and epinephrine are released; (**B**) these catecholamines act through β-adrenergic receptors to influence the spleen, lymph nodes, and tumor tissue, broadly affecting tumor cells and various immune cells: (**C**) dendritic cells (DCs), (**D**) Th1 cells, (**E**) $CD4^+$ T cells, (**F**) tumor cells, (**G**) macrophages, (**H**) myeloid-derived suppressor cells (MDSCs), (**I**) regulatory T cells (Tregs), (**J**) $CD8^+$ T cells, (**K**) B cells, and (**L**) natural killer (NK) cells, all of which are modulated to promote an immunosuppressive environment, facilitating tumor immune evasion and progression

glycolytic function [138, 139]. However, the application of β-blockers in colorectal cancer remains controversial. Some studies suggest that β-blockers reduce postoperative mortality and complications and improve immunotherapy outcomes [140–144], while others found no significant impact on colorectal cancer-specific mortality or even suggested an increased risk in advanced cases [145–147]. These contradictory findings highlight the complexity of neuro-immune-tumor interactions in peripheral solid tumors and underscore the need for further systematic studies to elucidate the precise

mechanisms by which sympathetic signaling influences tumor progression in different contexts.

Parasympathetic nervous system

The parasympathetic nervous system, primarily utilizing ACh as its neurotransmitter, plays a key regulatory role in modulating inflammatory responses and the TME. As the main efferent pathway of the parasympathetic system, the vagus nerve extensively innervates various visceral organs and significantly influences immune status through neuro-immune reflexes. Studies have shown that electrochemical stimulation of the vagus nerve can activate memory $CD4^+$ $ChAT^+$ T cells in the spleen, prompting them to release ACh. This ACh then acts on macrophages expressing acetylcholine receptors (AChRs) to suppress tumor necrosis factor-alpha (TNF-α) production, thereby exerting anti-inflammatory effects [46]. Moreover, this cholinergic signaling can also induce these T cells to secrete trefoil Factor 2 (TFF2), which exhibits significant inhibitory effects on colorectal cancer progression [47]. ACh primarily exerts multidimensional immune modulation by binding to nicotinic and muscarinic AChRs broadly expressed on immune cells [148].

Nicotinic ACh receptors (nAChRs), ligand-gated ion channels composed of five subunits forming a transmembrane protein complex, are mainly located on the plasma membrane and mitochondrial outer membrane [149]. Each subunit contains four conserved transmembrane domains, with a variable cytoplasmic loop between the third and fourth domains and N- and C-terminal regions extracellularly. When ACh or other agonists, such as nicotine, bind to nAChRs (mainly the α7 subunit) on the surface of immune cells, the receptor undergoes a conformational change, allowing a limited influx of cations such as calcium (Ca^{2+}) into the cell, which triggers intracellular signaling [150–152]. This Ca^{2+} influx can activate calmodulin-dependent signaling pathways, thereby regulating cell proliferation and survival [153]. In TAMs, activation of nAChRs significantly downregulates pro-inflammatory cytokines (e.g., TNF-α, IFN-γ, IL-1β, and IL-6), thereby dampening inflammatory signaling and alleviating chronic inflammation in the TME [48, 49] (Fig. 3A). In MDSCs, nAChR signaling enhances immunosuppressive function via upregulation of IL-10 [50] (Fig. 3B). Additionally, nAChRs can suppress the cytotoxic activity of $CD8^+$ T cells and NK cells by inhibiting granzyme and IFN-γ expression [52, 53] (Fig. 3C-D). Collectively, nAChR signaling tends to suppress both inflammatory and anti-tumor immune responses.

Muscarinic ACh receptors (mAChRs), members of the G-protein-coupled receptor (GPCR) family, are divided into five subtypes (M1R–M5R), encoded by the CHRM1 to CHRM5 genes. Based on their G protein coupling mechanisms, mAChRs can be grouped into two categories: M1, M3, and M5 subtypes couple with Gq proteins to activate the phospholipase C (PLC) pathway. PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2), producing inositol trisphosphate (IP3) and diacylglycerol (DAG), the latter activating protein kinase C (PKC) [154]. In contrast, M2 and M4 subtypes couple with Gi/Go proteins to inhibit adenylate cyclase (AC) activity, thereby reducing intracellular cyclic AMP (cAMP) levels [154]. The role of mAChRs in tumor immune regulation appears more complex [56]. Activation of mAChRs (e.g., with bethanechol) can significantly suppress tumor growth, accompanied by upregulation of pro-inflammatory cytokines and increased proliferation of tumor-associated epithelial cells ($CD44^+$) [54, 55]. Fujii et al. [155] found that M1 and M5 mAChR knockout mice showed significantly reduced antigen-specific IgG1 levels and secretion of pro-inflammatory cytokines (such as TNF-α, IFN-γ, and IL-6) after ovalbumin (OVA) immunization, indicating that mAChRs may enhance certain adaptive immune responses. Conversely, subsequent studies suggested that ACh released by the vagus nerve can suppress $CD8^+$ T cell activity via the M3 receptor (M3R), and selective deletion of the Chrm3 gene significantly inhibited liver tumor growth [51] (Fig. 3E). Furthermore, activation of mAChRs in Tregs can enhance their function and promote peripheral tissue infiltration, thereby preventing excessive immune responses [56]. However, mAChR expression in MDSCs is relatively low, and their functional role remains unclear [50].

Notably, recent studies have found that certain immune cells, such as $CD4^+$ T cells, can also synthesize and secrete ACh, forming an autonomous "immune cholinergic system," which may play a unique and critical role in tumor progression [156]. Despite growing interest in the potential role of the parasympathetic nervous system in cancer neuroimmunology, research in this area still lags behind that of the sympathetic system. This gap is partly due to the lack of efficient and specific tools for targeting parasympathetic input. In contrast, sympathetic nervous system studies often use chemical methods such as 6-hydroxydopamine to selectively ablate sympathetic fibers, facilitating investigations into their roles in tumor initiation, progression, and metastasis. The absence of pharmacological tools to selectively manipulate parasympathetic inputs remains a key limitation hindering further research. Moreover, parasympathetic preganglionic fibers mainly travel along the vagus nerve, which contains both sensory and motor components, introducing significant confounding factors in experimental interventions [157]. Adding to the complexity, research suggests that peripheral cancers may induce phenotypic changes in sensory neurons, enabling them to acquire sympathetic-like functions, thereby blurring functional distinctions

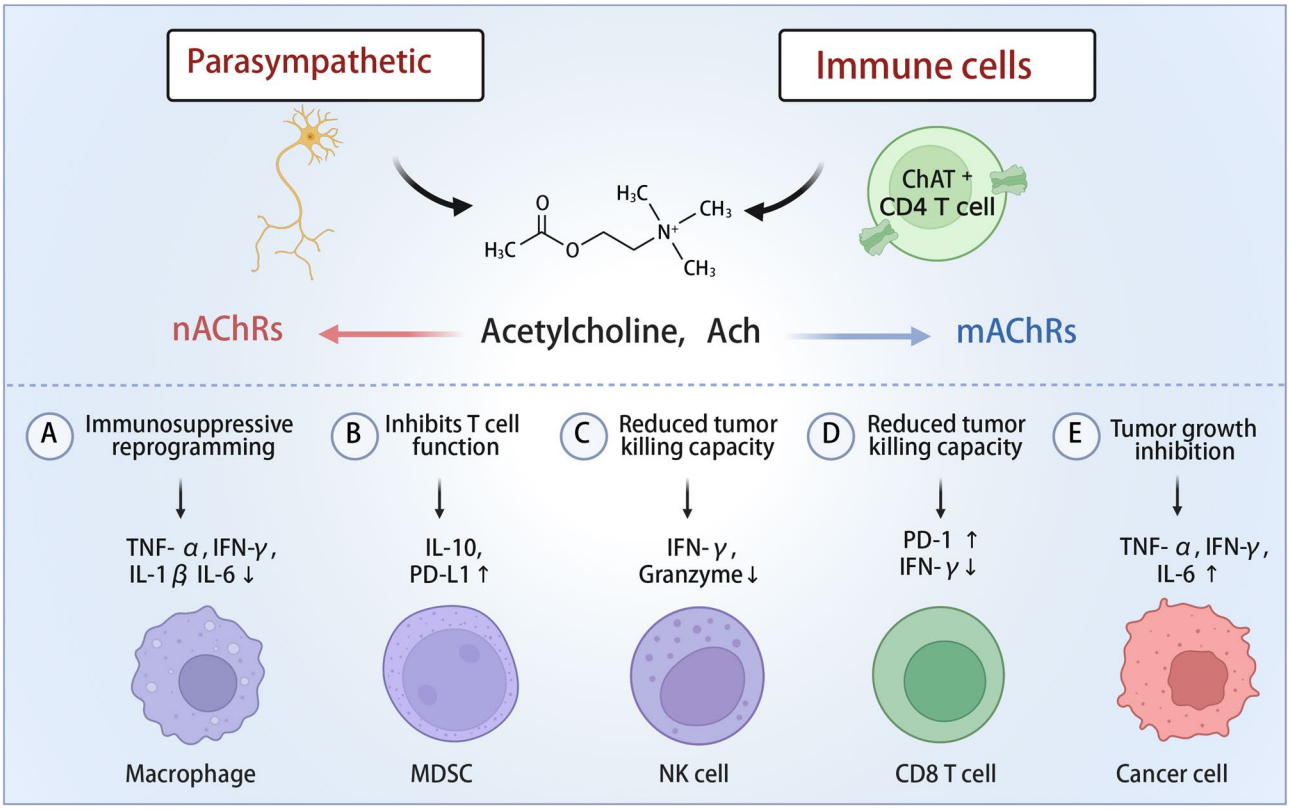


Fig. 3 Regulatory effects of acetylcholine on immune cells in the tumor microenvironment. Left: Acetylcholine is produced by parasympathetic neurons or ChAT⁺ CD4⁺ T cells, and modulates immune responses in the tumor microenvironment by binding to nicotinic (nAChRs) and muscarinic (mAChRs) acetylcholine receptors. Upper panel (red box): Acetylcholine derived from parasympathetic neurons binds to nAChRs on immune cells, exerting immunosuppressive effects. Specifically, (**A**) acetylcholine inhibits the expression of pro-inflammatory cytokines (e.g., TNF-α, IFN-γ) in macrophages, (**B**) induces myeloid-derived suppressor cells (MDSCs) to produce IL-10 and PD-L1, (**C**) reduces granzyme and IFN-γ levels in natural killer (NK) cells, and (**D**) upregulates PD-1 while reducing IFN-γ in CD8⁺ T cells, collectively suppressing anti-tumor immunity. Lower panel (blue box): Acetylcholine acts through mAChRs on various cell types in the tumor microenvironment. (**E**) In cancer cells, acetylcholine enhances pro-inflammatory cytokine expression and inhibits tumor growth

between neural types [158]. Thus, any surgical or physical manipulation involving the vagus nerve (e.g., vagotomy) often impacts not only parasympathetic output but also sensory and other neural pathways, complicating the interpretation of experimental outcomes.

Somatic nervous system

Nociceptors are a class of sensory nerve fibers capable of detecting harmful stimuli and playing critical roles in regulating immune and inflammatory responses [159]. Their terminals are distributed in peripheral tissues and, upon pathological stimulation, release a variety of neuropeptides, including Substance P and calcitonin gene-related peptide (CGRP) [160]. These molecules exert profound effects on both the innate and adaptive immune systems through binding to their specific receptors.

Substance P primarily signals through the neurokinin-1 receptor (NK1R) and exhibits pro-inflammatory effects across various immune cells. (Fig. 4A) It enhances the survival and activation of T lymphocytes, thereby promoting sustained effector function (Fig. 4B). Additionally, it induces macrophages to secrete multiple pro-inflammatory cytokines such as TNF-α and IL-1β, thereby amplifying local inflammatory responses (Fig. 4C). Substance P also upregulates the expression of the chemokine CCL5, enhancing the chemotaxis and migratory capacity of neutrophils, thus accelerating the recruitment of inflammatory cells to sites of tissue damage [57–59] (Fig. 4D). Consequently, within the TME, Substance P may drive immune cells toward a pro-inflammatory phenotype.

In contrast, CGRP exhibits more complex and bidirectional regulatory functions within the immune system. CGRP signals mainly through a receptor complex in which receptor activity-modifying protein 1 (RAMP1) is a critical component (Fig. 4E). RAMP1 is expressed in a variety of immune cells and is notably active within the TME [158, 161, 162]. In a syngeneic oral cancer model using CGRP knockout (CGRPKO) mice, infiltration of CD4⁺ T cells, CD8⁺ T cells, and NK cells into tumor tissue was significantly enhanced, and tumor growth was effectively suppressed (Fig. 4F). These findings support

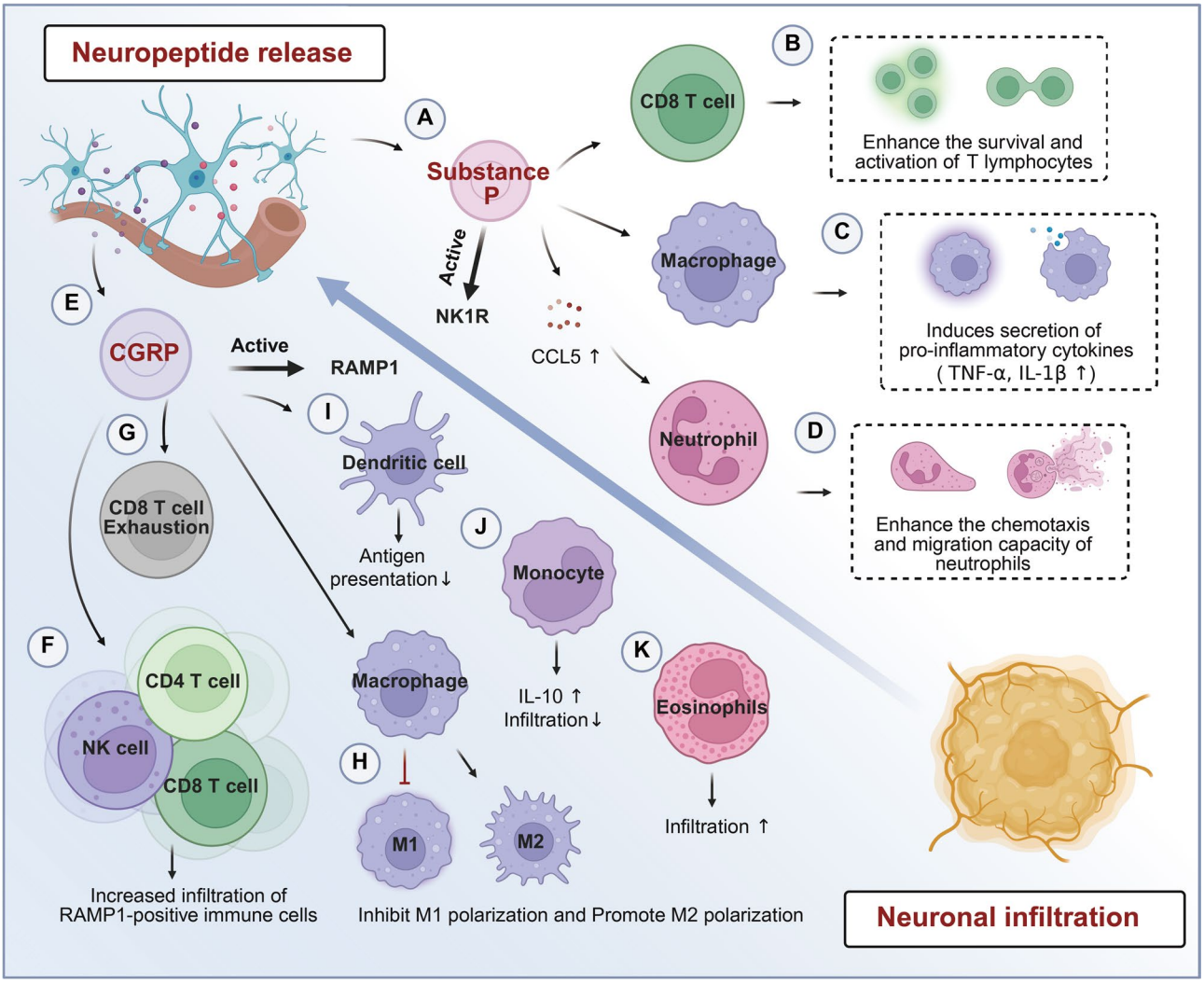


Fig. 4 Neuropeptide-mediated neuro-immune interactions regulating the tumor immune microenvironment. In the tumor microenvironment, (**A**) neurons release Substance P, which activates the neurokinin-1 receptor (NK1R), (**B**) enhances $CD8^+$ T cell survival and activation, (**C**) induces macrophages to secrete pro-inflammatory cytokines (e.g., TNF-α, IL-1β), and (**D**) promotes neutrophil chemotaxis and migration. (**E**) Neurons release CGRP, (**F**) which increases infiltration of RAMP1-positive $CD4^+$ T cells, $CD8^+$ T cells, and NK cells, (**G**) is associated with $CD8^+$ T cell exhaustion, (**H**) induces M2 polarization of macrophages, (**I**) inhibits dendritic cell antigen presentation, and (**J**, **K**) promotes infiltration of monocytes and eosinophils while upregulating IL-10

the notion that CGRP negatively regulates anti-tumor immunity to some extent [163, 164]. Similarly, in murine melanoma models, CGRP has been shown to induce functional exhaustion of $CD8^+$ T cells via the RAMP1 signaling pathway, reducing their cytotoxic activity and impairing anti-tumor responses (Fig. 4G). Pharmacological blockade of CGRP receptors or genetic deletion of TRPV1—a channel expressed in nociceptive sensory neurons—can attenuate sensory nerve signaling in the TME, alleviate $CD8^+$ T cell exhaustion, suppress tumor growth, and prolong survival [36, 60, 165]. Beyond its effects on T cells, CGRP also modulates innate immune cell function through various mechanisms. Studies have demonstrated that CGRP can downregulate the expression of inflammatory cytokines in macrophages and dendritic cells and suppress their antigen-presenting capacity, thereby impairing the initial activation of T cells [61] (Fig. 4I). Moreover, CGRP promotes the release of the anti-inflammatory cytokine IL-10 and inhibits NF-κB activity via the cAMP-PKA signaling pathway, reducing monocyte recruitment and ILC2 functionality, thereby helping to maintain mucosal homeostasis [61] (Fig. 4J). In macrophages, CGRP further promotes polarization toward the immunosuppressive M2 phenotype, inhibits the expression of NLRP3 inflammasomes and pro-IL-1β in M1 macrophages, and reduces pro-inflammatory responses, showing tissue-protective effects in acute lung injury models [61] (Fig. 4H). However, CGRP also exhibits pro-inflammatory properties under certain pathological conditions. It can promote the recruitment of

eosinophils and enhance T cell adhesion, thereby exacerbating local inflammation [62, 63] (Fig. 4K). In summary, sensory nerves play a critical role in immune regulation within the TME and hold significant potential as therapeutic targets.

Resident glial cells in the PNS

Schwann cells (SCs), essential components of the nerve sheath, have recently been found to play not only a pivotal role in nerve regeneration but also a complex regulatory role in tumor immunity within the TME [166]. Studies have shown that Schwann cells can secrete a variety of chemokines to promote the recruitment of immune cells into the TME, thereby modulating local immune responses [166]. In co-culture models with melanoma-conditioned media, activated GFAP⁺ Schwann cells significantly upregulate mRNAs associated with immune surveillance and inflammation regulation, such as IL-6, TGF-β, and VEGF [167]. Moreover, in co-culture experiments with cervical cancer cell lines (HeLa and ME180), chemokine CCL2 secreted by Schwann cells was found to influence tumor cell proliferation and promote the polarization of TAMs toward an immunosuppressive M2 phenotype, contributing to the formation of an immune-tolerant TME—a mechanism closely associated with poor prognosis in cervical cancer patients [168, 169] (Fig. 5A). Schwann cells also contribute to immune evasion and disease progression in cancers such as melanoma, pancreatic cancer, and prostate cancer by regulating the recruitment and function of MDSCs [169–171] (Fig. 5B). These immunosuppressive effects suggest that Schwann cells may, under certain circumstances, facilitate tumor progression.

Enteric glial cells (EGCs) are a distinct type of peripheral glial cell in the enteric nervous system (ENS), playing a crucial role in maintaining intestinal barrier integrity, regulating immune responses, and promoting intestinal repair and regeneration [172]. Recent studies have shown that EGCs also exhibit pro-tumorigenic effects in gastrointestinal cancers [173] (Fig. 5C). Under inflammatory stimuli, EGCs undergo morphological changes and upregulate GFAP expression [174]. In AOM/DSS and Apc^Min/+ mouse models, GFAP⁺ EGCs play a key pro-tumorigenic role in the early stages of colorectal cancer development [175]. Specific depletion of GFAP⁺ EGCs significantly reduces tumor number and size, suggesting their promoting role in tumor initiation. CRC cells preferentially adhere to and migrate along enteric neurons, a process mediated by L1CAM and N-cadherin [176]. Tumor epithelial cells (TECs) activate EGCs via IL-1, inducing a pro-tumor phenotype, and promote cancer stem cell (CSC) expansion and CSC-driven tumorigenesis through the PGE2/EP4/EGFR pathway [177]. Inhibition of IL-1 in TECs or blockade of PGE2 in EGCs effectively prevents this pro-tumorigenic transformation [175]. Additionally, EGCs secrete NGF, BDNF, GDNF, and NT-3, which promote neuronal growth and cancer cell migration, with the GDNF/GFRα1 axis closely associated with CRC invasion and poor prognosis [178–181]. In the tumor immune microenvironment (TIME), EGCs respond to IL-1 by secreting IL-6, driving monocytes to differentiate into pro-tumor SPP1 macrophages, thereby promoting CRC progression [182]. In summary, EGCs contribute to tumor development and progression by directly promoting tumor cell proliferation, CSC expansion, and modulating the immune microenvironment.

CNS neurotransmitter-mediated peripheral immune regulation

The glutamate system

Glu is the principal excitatory neurotransmitter in the mammalian central nervous system, and its extracellular concentration is tightly regulated to prevent excitotoxicity. As a non-essential amino acid, glutamate not only participates in various metabolic processes, but can also be converted into α-ketoglutarate (α-KG) in the tricarboxylic acid (TCA) cycle via glutaminase (GLS), glutamate dehydrogenase (GDH), and aspartate aminotransferase (AAT) [183, 184]. In addition, glutamate serves as a key precursor for glutathione (GSH) synthesis and is thus critical for maintaining cellular redox homeostasis [185, 186]. Glutamate signals through specific receptors, which are classified into ionotropic receptors (iGluRs, including NMDAR, AMPAR, and KAR) and metabotropic receptors (mGluRs, eight G protein-coupled receptors of which mGluR1/2/3/5 couple to Gq and mGluR4/6/7/8 couple to Gi) [187]. Recent studies have shown that immune cells also express glutamate receptors, suggesting that glutamate signaling may play a role in immune cell differentiation, activation, and functional regulation [188, 189].

Metabotropic glutamate receptors are widely expressed in various immune cells and play a critical role in regulating immune responses [190]. mGluRs can be activated by glutamate or synthetic agonists, subsequently influencing cellular functions via modulation of G protein signaling pathways. mGluR4, for instance, is expressed in DCs. Overexpression of mGluR4 suppresses the expression of co-stimulatory molecules CD80 and CD86. Conversely, knockdown of mGluR4 in bone marrow-derived DCs significantly enhances the production of IL-6, IL-17 A, and IL-23 [64]. In non-tumor models, curcumin as an agonist can suppress the secretion of IL-6 and IL-23, thereby inhibiting Th17 cell differentiation [65]. Previous studies also indicate that mGluR4 regulates the expression of IL-12 and IL-23, playing a significant role in tumor immune modulation [66]. In osteosarcoma models, IL-23 promotes tumor progression, while IL-23

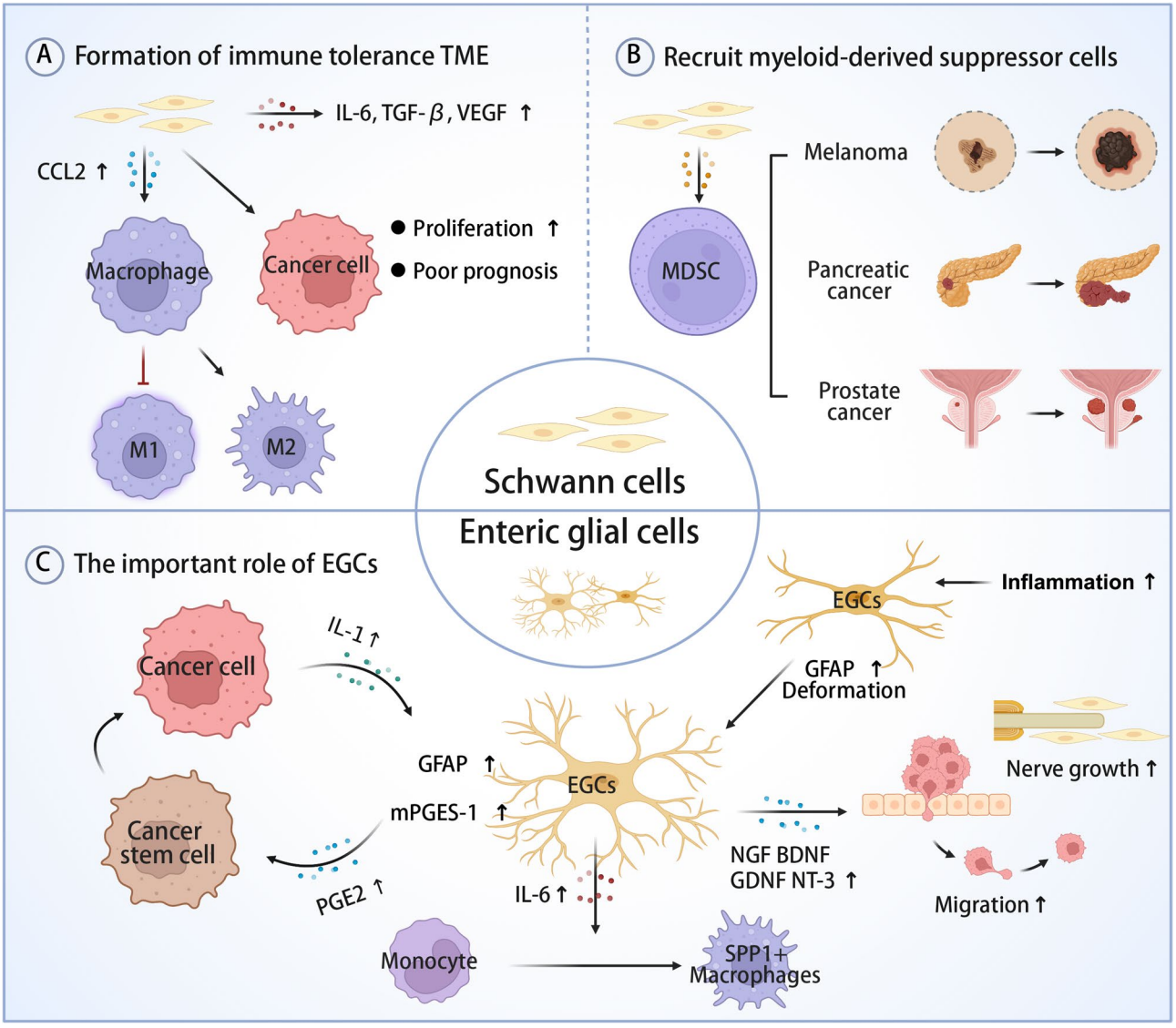


Fig. 5 Roles of Schwann cells and enteric glial cells (EGCs) in the tumor microenvironment. (**A**) Formation of an immune-tolerant microenvironment: Schwann cells upregulate CCL2, IL-6, TGF-β, and VEGF, promoting the polarization of macrophages toward the M2 phenotype, enhancing tumor proliferation, and correlating with poor prognosis. (**B**) Recruitment of myeloid-derived suppressor cells (MDSCs): Schwann cells recruit MDSCs, contributing to the formation of an immune-suppressive microenvironment in melanoma, pancreatic cancer, and prostate cancer. (**C**) Key roles of EGCs: Under inflammatory stimuli, EGCs change morphology and upregulate GFAP expression. Tumor epithelial cells (TECs) activate EGCs via IL-1, inducing a pro-tumor phenotype. Activated EGCs promote cancer stem cell (CSC) expansion through PGE2, thereby driving CSC-mediated tumorigenesis. In addition, EGCs respond to IL-1 by secreting IL-6, which drives monocytes to differentiate into pro-tumor SPP1 macrophages. EGCs also secrete neurotrophic factors NGF, BDNF, GDNF, and NT-3, promoting nerve growth and enhancing cancer cell migration

deficiency or neutralization therapy effectively inhibits tumor growth. Notably, mGluR4 selectively suppresses IL-23 expression in tumor-associated myeloid cells [66, 191]. Recent research has revealed that mGluR4 is also widely expressed in T cells and NK cells. Single-cell RNA sequencing and flow cytometry have confirmed mGluR4 expression in $CD4^+$ T cells, $CD8^+$ T cells, and NK cells across various tumor models including B16F10, 3LL, and MC38 [67]. In $Grm4^{-/-}$ mice, tumor growth is significantly suppressed, accompanied by enhanced infiltration and proliferation of $CD8^+$ T cells and NK cells within the TME. Moreover, the CD8-C7-Itgb1 subpopulation exhibits markedly increased IFN-γ production. mGluR4 negatively regulates immune function through inhibition of the cAMP signaling pathway. Its deficiency leads to upregulated cAMP levels, which in turn enhance the antitumor responses of $CD8^+$ T cells and NK cells, alongside elevated expression of pCREB and IFNGR1 [67, 192]. Interestingly, pharmacological inhibition of mGluR4 using the selective antagonist MSOP in wild-type mice mimics the immune-enhancing effects seen in $Grm4^{-/-}$ mice, further validating mGluR4 as a critical negative

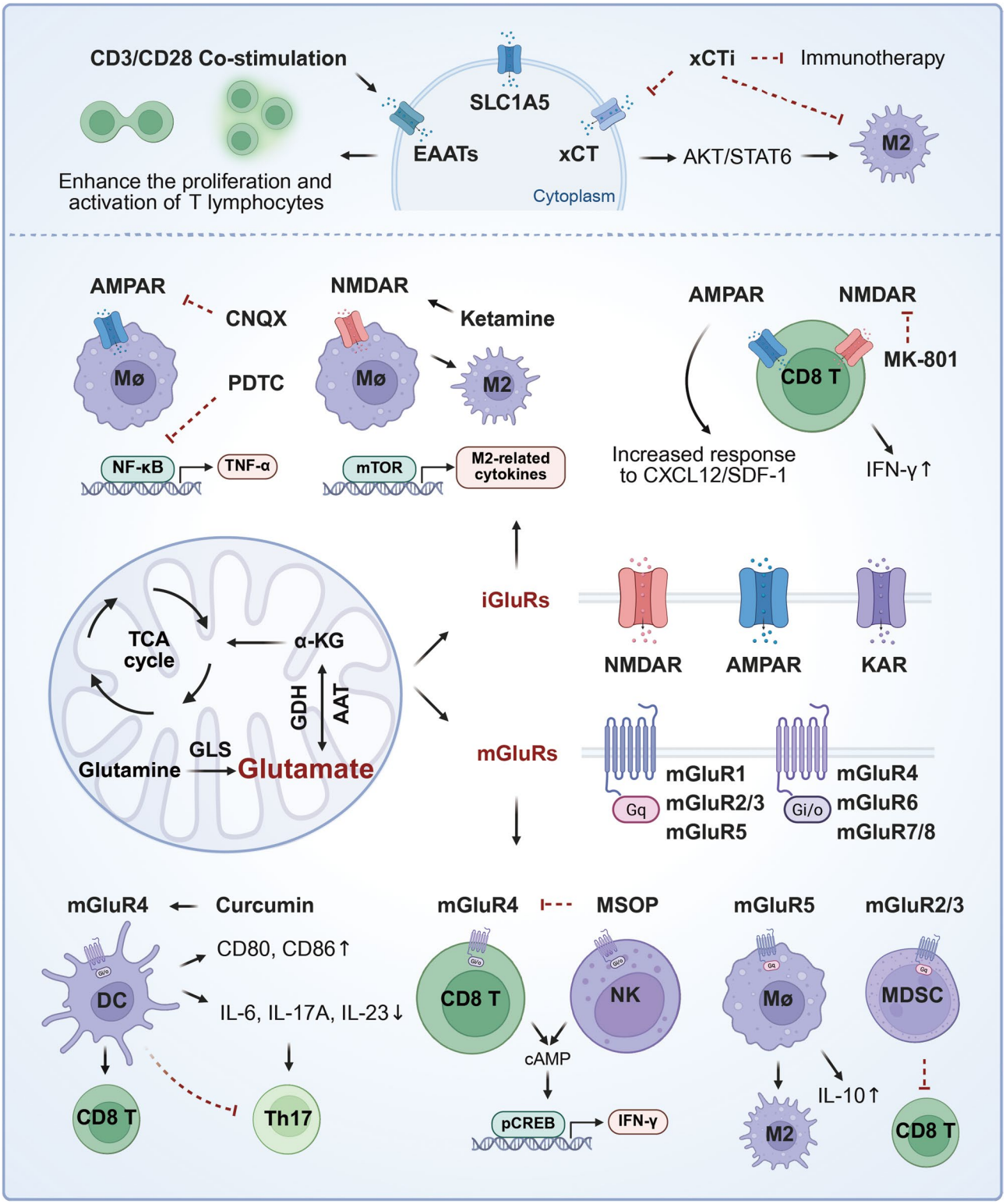


Fig. 6 (See legend on next page.)

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Fig. 6 Mechanisms of glutamate metabolism and its receptors in tumor immune regulation. Upon CD3/CD28 co-stimulation, T cells activate transporters such as SLC1A5, EAATs, and xCT to mediate the transmembrane transport of glutamate and glutamine, promoting T cell proliferation and activation. Glutamine can be converted to glutamate via glutaminase (GLS), and subsequently transformed into α-ketoglutarate (α-KG) through glutamate dehydrogenase (GDH) or aminotransferases (AAT), feeding into the TCA cycle to maintain metabolic homeostasis. Inhibition of xCT (xCTi) can block the AKT/STAT6 signaling pathway, suppress M2 macrophage polarization, and enhance the efficacy of immunotherapy. Glutamate regulates immune cell function through activation of two receptor types: Ionotropic glutamate receptors (iGluRs) include NMDAR, AMPAR, and KAR. AMPAR activation in macrophages promotes the NF-κB/TNF-α pathway, modulating the expression of inflammatory cytokines. In $CD8^+$ T cells, it enhances responses to the chemokine CXCL12/SDF-1 and increases IFN-γ secretion. Conversely, NMDAR activation induces M2c-like macrophage polarization and suppresses the expression of pro-inflammatory cytokines such as IFN-γ in IL-2-activated T cells. Metabotropic glutamate receptors (mGluRs) include mGluR1–8, categorized into three groups based on their coupled G proteins. Enhanced mGluR4 signaling (e.g., via curcumin treatment) promotes dendritic cell maturation, boosts $CD8^+$ T cell activity, and suppresses Th17 responses. It negatively regulates cAMP signaling; mGluR4 deficiency leads to increased cAMP, further activating antitumor functions of $CD8^+$ T cells and NK cells. mGluR5 promotes M2 macrophage polarization. mGluR2/3 enhance IL-10 secretion in MDSCs, inhibiting $CD8^+$ T cell activity

regulator of antitumor immunity [67]. In RAW264.7 macrophages, overexpression of mGluR5 has been shown to upregulate IL-10 levels, an effect associated with increased expression of PPAR-γ. This suggests that mGluR5 may promote macrophage polarization toward the M2 immunosuppressive phenotype through a PPAR-dependent transcriptional mechanism [68, 69]. In contrast, in myeloid-derived suppressor cells, antagonism of mGluR2/3 using LY341495 significantly reduces their immunosuppressive activity and inhibits B16F10 tumor growth. This indicates that mGluR2/3 may modulate tumor immune responses by regulating MDSCs function [71]. Overall, these findings highlight the diverse and subtype-specific immunomodulatory roles of mGluRs in the TME. While receptors like mGluR4 and mGluR2/3 act as negative regulators of antitumor immunity, their inhibition presents promising avenues for cancer immunotherapy. (Fig. 6)

Recent studies have shown that iGluRs also play important regulatory roles in immune cells, although their involvement within the TIME has been less well explored. In macrophages, the role of AMPA receptors has been clearly demonstrated. In RAW264.7 cells, activation of AMPARs significantly enhances the expression of the pro-inflammatory cytokine TNF-α, accompanied by the activation of the nuclear factor NF-κB. Treatment with the AMPAR antagonist CNQX suppresses TNF-α production, and the NF-κB inhibitor pyrrolidine dithiocarbamate (PDTC) also reduces TNF-α levels, suggesting that AMPARs may regulate macrophage-mediated pro-inflammatory responses via the NF-κB pathway [72]. Additionally, ketamine, a rapid-acting NMDAR agonist primarily known for its effects in the central nervous system—particularly its activation of the mTOR pathway to promote synaptic plasticity—has been found to affect the peripheral immune system as well. Ketamine treatment induces macrophages to polarize toward an M2c-like phenotype, characterized by increased expression of CD163 and Mer tyrosine kinase (MERTK), along with decreased expression of activation markers CD80 and HLA-DR [70]. In T cells, activation of AMPARs promotes chemotactic migration toward the chemokine CXCL12/SDF-1 [73]. Meanwhile, the NMDAR antagonist MK-801 significantly inhibits intracellular calcium influx in T cells [76]. Stimulation of NMDARs by glutamate has been shown to suppress the expression of inflammatory cytokines such as IFN-γ in IL-2–activated T cells. However, some studies also indicate that under certain physiological conditions, glutamate can enhance inflammatory cytokine production [76]. Although these findings were obtained in non-tumor models, they provide valuable insights for studies conducted in the context of cancer. (Fig. 6)

In addition to direct regulation at the receptor level, glutamate and its metabolic pathways indirectly modulate antitumor immunity by influencing immune cell metabolism. Following T-cell activation, the expression of excitatory Amino Acid Transporters (EAATs) and SLC1A5 is upregulated to enhance glutamine/glutamate uptake, which is essential for T-cell function [74, 75]. Similarly, in naïve $CD4^+$ T cells, T cell receptor (TCR) stimulation induces upregulation of the glutamine transporter SLC1A5, further promoting glutamine uptake to support T cell proliferation and function [74]. In addition to EAATs, the glutamate–cystine antiporter xCT also plays an important role in tumor immune regulation. In mouse models, both pharmacological inhibition and genetic knockout of xCT significantly suppress melanoma cell proliferation. However, it is worth noting that combining xCT inhibition with immune checkpoint blockade (e.g., anti–PD-1/PD-L1 therapy) paradoxically weakens the efficacy of PD-1/PD-L1 blockade. Mechanistic studies suggest that this suppressive effect may arise from xCT inhibition impairing the cytotoxic function of $CD8^+$ T cells and promoting M2-like polarization of macrophages [193]. Although the mechanisms by which xCT inhibition affects the efficacy of immunotherapy remain incompletely understood, one possible explanation is that xCT inhibition alters extracellular concentrations of glutamate and cystine, thereby affecting immune cell functionality and tumor–immune interactions [193]. Recent studies further reveal that high xCT expression in TAMs is strongly associated with poor prognosis in lung cancer patients and inversely correlated with the degree of TAM

infiltration, suggesting that xCT may promote tumor progression by regulating TAM polarization [194]. While xCT deletion in macrophages does not significantly alter their infiltration into tumor tissues, it can inhibit M2 polarization via downregulation of the AKT/STAT6 signaling pathway, and enhance $CD8^+$ T cell infiltration and accumulation within the tumor, thereby promoting antitumor immune responses [194]. (Fig. 6)

Although current research has made progress in elucidating the roles of GluRs in cancer development and immune regulation, many questions remain unresolved. For example, some pharmacological modulators of GluRs have demonstrated promising anti-tumor effects in animal models, but clinical trial data remain limited. In addition, whether different GluR subtypes cooperate within the tumor microenvironment or whether mutations in specific GluR genes might drive tumorigenesis remains poorly understood. Further exploration of these questions will provide a stronger theoretical foundation for targeted intervention in glutamate signaling pathways for cancer immunotherapy.

Serotonin

5-HT, also known as serotonin, was originally discovered in serum, hence its name. It is secreted not only by the central nervous system and enterochromaffin cells in the gut, but also synthesized locally by various cells in the skin [195] (Fig. 7). Approximately 95% of systemic serotonin is present in the gastrointestinal tract, while less than 5% is present in the CNS and other organs [196]. During biosynthesis, tryptophan, an essential amino acid, is first converted into 5-hydroxytryptophan (5-HTP) by

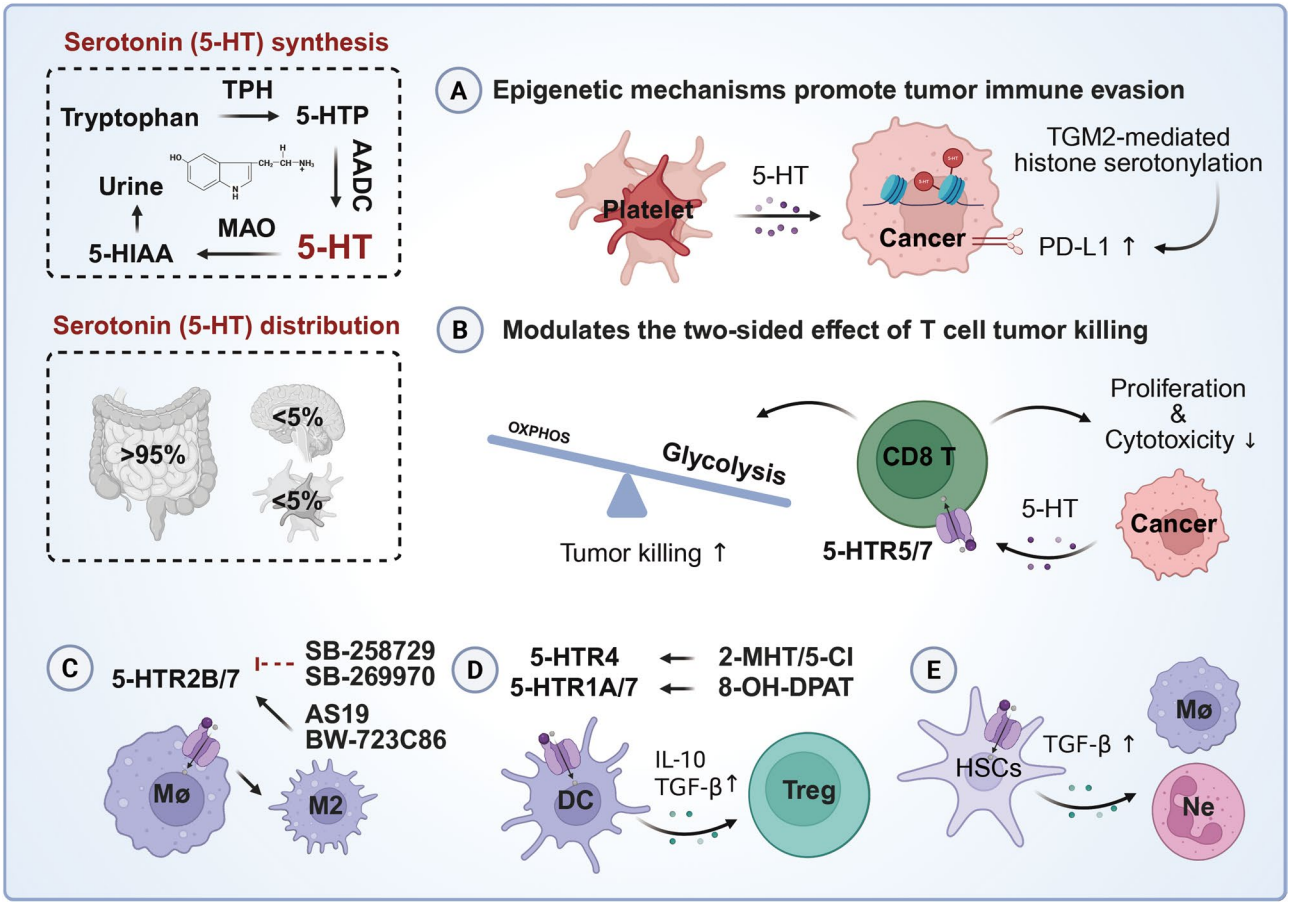


Fig. 7 Multifaceted roles of serotonin in tumor immune regulation. Serotonin is synthesized from tryptophan via tryptophan hydroxylase (TPH) and aromatic L-amino acid decarboxylase (AADC), and subsequently degraded by monoamine oxidase (MAO) into 5-HIAA. The serotonin transporter (SERT) recycles serotonin from the synaptic cleft back into neurons. Selective serotonin reuptake inhibitors (SSRIs) can effectively enhance T cell-mediated antitumor immune responses. Over 95% of 5-HT is stored in the gut, with small amounts present in the central nervous system and blood. Its roles in tumor immunity include: (**A**). Platelet-released 5-HT promotes histone serotonylation via tissue transglutaminase 2 (TGM2), upregulating PD-L1 expression in cancer cells and facilitating immune evasion. (**B**). $CD8^+$ T cells sense 5-HT via 5-HTR5 and 5-HTR7, modulating the balance between oxidative phosphorylation and glycolysis, thereby enhancing their cytotoxic function. However, 5-HT can also suppress T cell proliferation and cytotoxicity, weakening immune responses. (**C**). Activation of 5-HTR2B or 5-HTR7 induces M2 macrophage polarization, promoting an immunosuppressive phenotype. (**D**). 5-HT acts on dendritic cells via 5-HTR4 or 5-HTR1A/7, inducing IL-10 and TGF-β secretion and contributing to immune tolerance. (**E**). 5-HT stimulates hepatic stellate cells (HSCs) to produce TGF-β, which drives macrophages and neutrophils toward immunosuppressive phenotypes

the enzyme tryptophan hydroxylase (TPH), and then transformed into 5-HT by aromatic L-amino acid decarboxylase (AADC). The synthesized 5-HT is primarily stored in the CNS, platelets, and gastrointestinal tract, and is eventually metabolized by monoamine oxidase (MAO) into 5-hydroxyindoleacetic acid (5-HIAA), subsequently eliminated via the urine [197]. TPH is encoded by two genes: TPH1, which is predominantly expressed in peripheral tissues (e.g., gut, skin) and to a lesser extent in the pineal gland and CNS, and TPH2, which is specifically expressed in neurons and serves as the primary enzyme for neuronal 5-HT synthesis [198]. Serotonin receptors (5-HT receptors) are a class of receptors that bind 5-HT and mediate its biological effects. They are divided into seven major classes (5-HTR1 through 5-HTR7). Although serotonin is primarily recognized for its function as a neurotransmitter in the CNS, accumulating evidence indicates that it also has important biological functions in the immune system. Peripheral serotonin can be taken up and stored by platelets, where it modulates both inflammatory processes and immune function. For instance, in mouse orthotopic xenograft models of gastric and pancreatic cancers, 5-HT originating from platelets enhances PD-L1 expression on tumor cells via histone serotonylation catalyzed by transglutaminase 2 (TGM2), thus facilitating immune evasion through epigenetic regulation [77] (Fig. 7A). In inflammatory environments, T cells can upregulate 5-HT7 receptor expression, leading to the production of the anti-inflammatory cytokine IL-10, thereby attenuating the inflammatory responses [199]. Furthermore, A549 lung cancer cells, which exhibit a neuroendocrine phenotype, are capable of secreting 5-HT and suppressing cytotoxic T lymphocyte proliferation via activation of 5-HT5A and 5-HT7 receptors [78] (Fig. 7B). Recent studies have revealed that $CD8^+$ T cells can accumulate intracellular 5-HT through two mechanisms: (1) intracellular synthesis via TPH1; and (2) uptake from the extracellular environment via the serotonin transporter (SERT). Meanwhile, monoamine oxidase A (MAOA) catalyzes the breakdown of intracellular 5-HT, serving as an intrinsic suppressor of $CD8^+$ T cell activity. During serotonylation, TGM2 covalently links 5-HT to glutamine residue 262 of GAPDH, promoting its cytoplasmic localization. This shift drives glycolysis in $CD8^+$ T cells, thereby enhancing their anti-tumor immune function [79]. The SERT is a key molecule that regulates serotonin levels and its physiological functions. Accumulating evidence indicates that pharmacological blockade of SERT with selective serotonin reuptake inhibitors (SSRIs)—commonly prescribed antidepressants—can markedly inhibit tumor progression and potentiate T cell-mediated antitumor immunity across multiple murine syngeneic and human xenograft models [200]. Beyond T cells, serotonin exerts broad regulatory effects on various immune cells. For example, activation of 5-HTR2B and 5-HTR7 receptors promotes M2-type anti-inflammatory macrophage polarization, a subtype often associated with pro-tumor functions [80, 81] (Fig. 7C). 5-HT can also promote the maturation and chemotaxis of bone marrow–derived dendritic cells and drive their differentiation into anti-inflammatory phenotypes, which in turn promotes the conversion of T cells into Tregs [82–84]. Tregs are known to suppress CTL activity and thereby facilitate tumor immune evasion [201]. Research by Duerschmied et al. demonstrated that platelet-derived 5-HT inhibits the migration of neutrophils and monocytes to sites of inflammation. In the absence of peripheral 5-HT, leukocyte rolling on the endothelium significantly increases, indicating serotonin's key role in innate immune cell trafficking [85]. In liver cancer models, 5-HT activates hepatic stellate cells (HSCs), inducing the secretion of TGF-β1, which enhances pro-tumor functions of neutrophils and macrophages [202, 203] (Fig. 7E). Notably, newly developed 5-HT-loaded nanoparticles can target myeloperoxidase activity and effectively inhibit neutrophil-mediated lung tumor metastasis [204, 205]. Taken together, serotonin signaling exhibits an overall immunosuppressive tendency across multiple immune cell types, thereby facilitating tumor initiation and progression. Targeting the serotonin system with psychiatric drugs or other small molecules may hold therapeutic potential in cancer immunotherapy.

Currently, 15 subtypes of 5-HT receptors (5-HTRs) have been identified and are widely expressed on immune cells, stromal cells, and tumor cells. Several 5-HTR agonists have been shown to regulate immune function. For instance, BW-723C86 (a 5-HTR2B agonist) and AS19 (a 5-HTR7 agonist) induce anti-inflammatory polarization in macrophages [81, 206]. Meanwhile, several compounds—including AnHCl (targeting 5-HTR1B), BRL5443 (acting on 5-HTR1E/1F), and DOI (a 5-HTR2 agonist)—have been reported to enhance DC activity [207]. Furthermore, secretion of pro-inflammatory cytokines such as IL-8 and IL-1β from DCs is promoted by 8-OH-DPAT (a 5-HTR1A/7 agonist), 2-methylserotonin (5-HTR3), and 5-CI and 2-MHT (both targeting 5-HTR4) [207] (Fig. 7D). Additionally, 5-HTR3 and 5-HTR7 agonists can stimulate T cell activation and proliferation [208, 209]. On the antagonist side, 5-HTR7 antagonists SB-269,970 and SB-258,729 have been extensively studied and are shown to inhibit M2 macrophage polarization, modulate cytokine secretion by DCs, and suppress the ERK signaling pathway in T cells [80, 83, 206–208]. The 5-HTR1A antagonist SB-216,641 shows similar regulatory effects on T cells as 5-HTR7 antagonists [208]. Broad-spectrum antagonists, such as methylsergide and ketanserin, can suppress DC activation and

T cell–mediated delayed-type hypersensitivity reactions [210] In summary, serotonin and its receptors orchestrate multifaceted, multi-target immune regulation. Targeting specific 5-HTR subtypes and their downstream signaling pathways holds promise for developing novel therapeutic strategies and drug targets for malignant tumors and other immune-related diseases.

Dopamine signaling

DA is a monoamine neurotransmitter primarily found in the CNS, and in recent years it has been recognized as a key regulator in neuro-immune interactions, influencing the TME and the initiation and progression of cancer (Fig. 8). Accumulating evidence demonstrates that DA not only regulates CNS function but also exerts diverse biological effects on the peripheral immune system via multiple receptor subtypes. Various immune cells—including effector T cells, Tregs, NK cells, B cells, neutrophils, macrophages, monocytes, and DCs—express dopamine receptors (DRs) [211]. Based on their signaling mechanisms, dopamine receptors are classified into two major families: D1-like receptors (D1R and D5R), which couple with Gs proteins to activate adenylyl cyclase and promote cell activation, and D2-like receptors (D2R, D3R, and D4R), which couple with Gi proteins to exert inhibitory regulatory effects. Notably, DA synthesis is not restricted to the CNS; it also occurs in peripheral tissues such as the gastrointestinal tract, spleen, and pancreas [212]. In lung cancer patients, plasma DA concentrations can increase up to fivefold compared to normal levels, reaching thresholds that exert significant immunomodulatory effects. In vitro studies have shown that this concentration of DA significantly inhibits T cell proliferation and cytotoxic activity—an effect mainly mediated by D1-like receptors and reversible with the D1R/D5R-selective antagonist SCH23390 [87]. In colorectal cancer models, the DRD2 antagonist trifluoperazine (TFP) was found to upregulate PD-L1 expression on tumor cells and significantly increase the expression of PD-1 on $CD4^+$ and $CD8^+$ T cells in the tumor microenvironment [88]. In TAMs, DA activates D4R to enhance the anti-tumor efficacy of gemcitabine in pancreatic ductal adenocarcinoma and reduces the number of $CD206^+$ M2 macrophages. This effect may be mediated through the

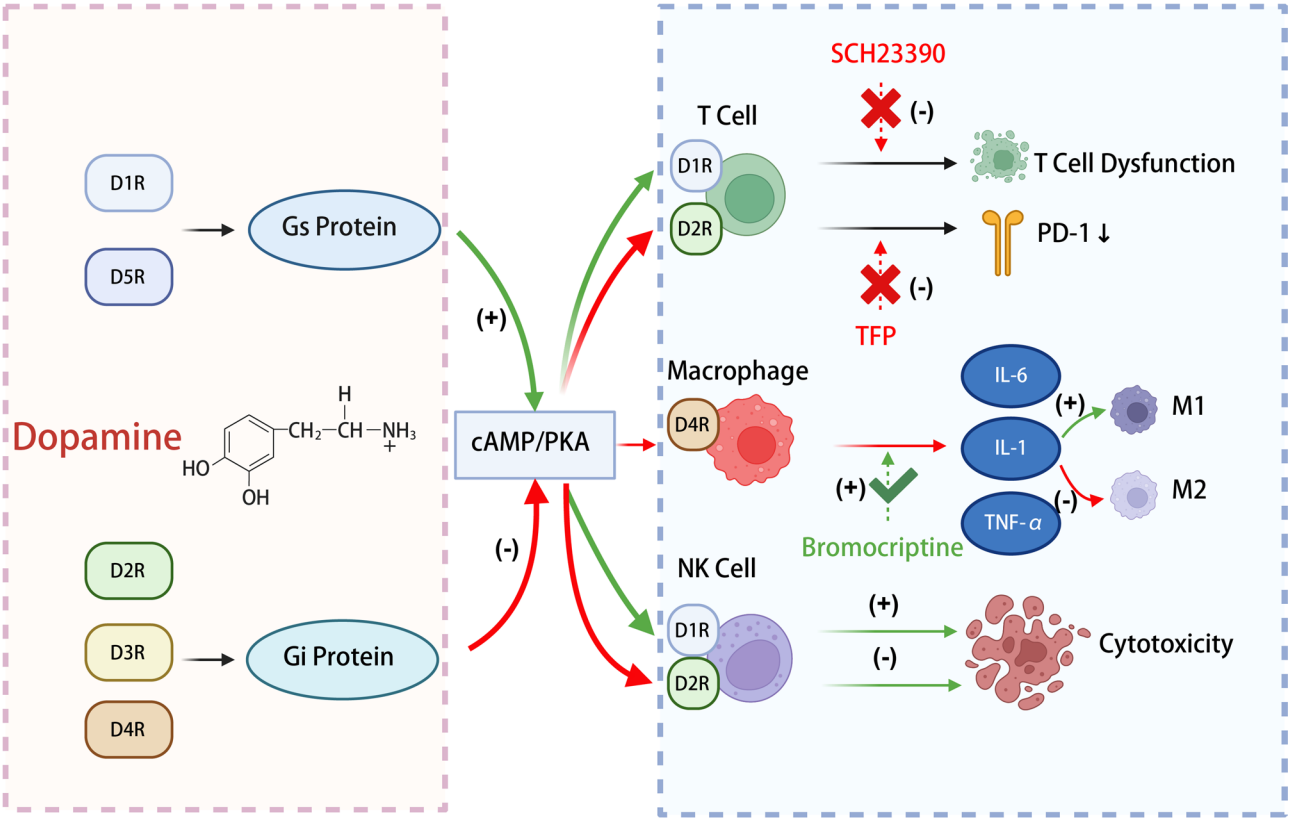


Fig. 8 Mechanisms of dopamine-mediated regulation of immune cell functions. Dopamine interacts with five receptor subtypes (D1R–D5R), activating Gs- or Gi-coupled pathways to regulate intracellular cAMP/PKA signaling, thereby modulating the functions of T cells, macrophages, and NK cells: D1R and D5R activate Gs proteins to increase cAMP/PKA signaling. D2R, D3R, and D4R activate Gi proteins to inhibit this pathway. T cells: D1R signaling impairs T cell function; its antagonist SCH23390 can reverse this effect. D2R signaling downregulates PD-1 expression. Macrophages: D4R signaling enhances pro-inflammatory cytokine expression (IL-6, IL-1, TNF-α), promotes M1 polarization, and inhibits M2 immunosuppressive polarization. NK cells: D1R enhances NK cytotoxicity, whereas D2R reduces it

cAMP/PKA pathway leading to downregulation of IL-1 expression, without significantly affecting TNF-α levels [89]. DA also inhibits TAM recruitment and reduces the expression of pro-inflammatory factors such as IL-6 and TNF-α. Dopaminergic agonists (e.g., bromocriptine) can induce apoptosis in breast cancer cells and inhibit tumor growth through the same signaling mechanisms [90, 91]. Dopamine's role in regulating MDSCs has also garnered attention. Studies have shown that intraperitoneal injection of Escherichia coli activates dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain, promoting both innate and adaptive immune responses through sympathetic nervous system signaling [213]. Further experiments revealed that pharmacological activation of the VTA can suppress the growth of B16 melanoma and Lewis lung carcinoma via MDSCs-dependent mechanisms [214]. In peripheral animal models, systemic administration of DA activated D1-like receptors on Gr-1$^+$CD115$^+$ MDSCs, suppressing IFN-γ-induced ERK and JNK signaling and nitric oxide (NO) synthesis, thereby mitigating their immunosuppressive effects on T cells and enhancing anti-tumor immunity [92]. Additionally, NK cells express all subtypes of dopamine receptors. Activation of D1R enhances their cytotoxicity against YAC-1 lymphoma cells via the cAMP/PKA/CREB pathway, whereas the D2R agonist quinpirole can antagonize this effect [93]. NK cells derived from dopamine transporter (DAT)-deficient mice exhibit significantly reduced proliferation and cytokine secretion, further confirming the negative regulatory role of DA on NK cell function [214, 215]. In conclusion, dopamine mediates complex signaling networks via its multiple receptors on immune cells, broadly regulating the TIME and impacting tumor development, progression, and therapeutic response.

GABAergic signaling

GABA, the main inhibitory neurotransmitter in the CNS, is additionally prevalent in peripheral tissues. GABA exerts its biological functions mainly through two classes of receptors: the ligand-gated ionotropic GABA_A receptors, which mediate neuronal inhibition by facilitating chloride (Cl^-) influx, and the G protein-coupled metabotropic GABA_B receptors, which participate in various signaling pathways via coupling with Gi proteins (Fig. 9). In recent years, GABA has attracted increasing attention as a potential "oncometabolite" involved in the initiation, progression, and metastasis of various cancers—particularly in brain metastases [216]. Studies have shown that inhibition of GABA synthesis or its signaling pathways can enhance anti-tumor immune activity, thereby promoting tumor clearance [95, 217, 218]. The presence of GABAergic signaling pathways has been confirmed in various immune cell types, including T cells, B cells, NK cells, macrophages, and DCs, where GABA can regulate critical immune functions such as cytokine secretion, activation, cell migration, and cytotoxicity [219–221]. For instance, it has been found that the GABA_A receptor subunit GABRP is significantly upregulated during the malignant progression of pancreatic cancer and is closely associated with poor prognosis [218]. Moreover, increased GABRP expression is positively correlated with high macrophage infiltration in tumor tissues, which is widely recognized as promoting tumor advancement through the inhibition of immune effector cell activity [94]. Mechanistically, GABRP can regulate intracellular calcium levels in pancreatic cancer cells via a GABA-independent pathway, thereby triggering the NF-κB pathway, promoting pro-inflammatory cytokine expression, and promoting the recruitment of tumor-associated macrophages. Another study further revealed a mechanism by which cancer cell-derived GABA contributes to immune evasion. It was found that GABA secreted by cancer cells is not used as a metabolic substrate or building block, but instead activates GABA_B receptors to stabilize β-catenin, thereby suppressing the expression of chemokines CCL4 and CCL5 and blocking the recruitment of dendritic cells [95]. Given that DCs are essential for initiating T cell-driven inflammatory responses in the TME, this mechanism shifts the TME toward an immunologically "cold" state, facilitating immune evasion and tumor growth [222]. Interestingly, B cells have also been found to synthesize and secrete GABA, exerting immunomodulatory functions in the TME [217]. Specifically, GABA derived from B cells can inhibit the cytolytic activity of CD8$^+$ T cells and promote the differentiation and persistence of anti-inflammatory macrophages, thereby further attenuating the anti-tumor immune response. In addition to indirectly affecting immune function via cytokine regulation, GABA itself may act as a chemotactic factor, directly participating in the migration and functional regulation of immune cells within the TME [96]. Based on these findings, targeting GABA signaling is increasingly recognized as a compelling immunotherapy approach, with the potential to improve the clinical effectiveness of treatments such as immune checkpoint blockade. One study using immunocompetent tumor-bearing mouse models demonstrated that combination therapy with the GABA_B receptor antagonist 2-OH-saclofen and anti-PD-1 monoclonal antibody markedly suppressed tumor progression and prolonged survival more effectively than either monotherapy [95]. This result is consistent with earlier findings that GABA_B receptor activation has anti-inflammatory effects [223, 224]. As our understanding of the expression of GABAergic components in immune cells and their role in inflammation deepens [219], future research may enable more precise anti-tumor immune regulation strategies through selective targeting of different GABA receptor subtypes

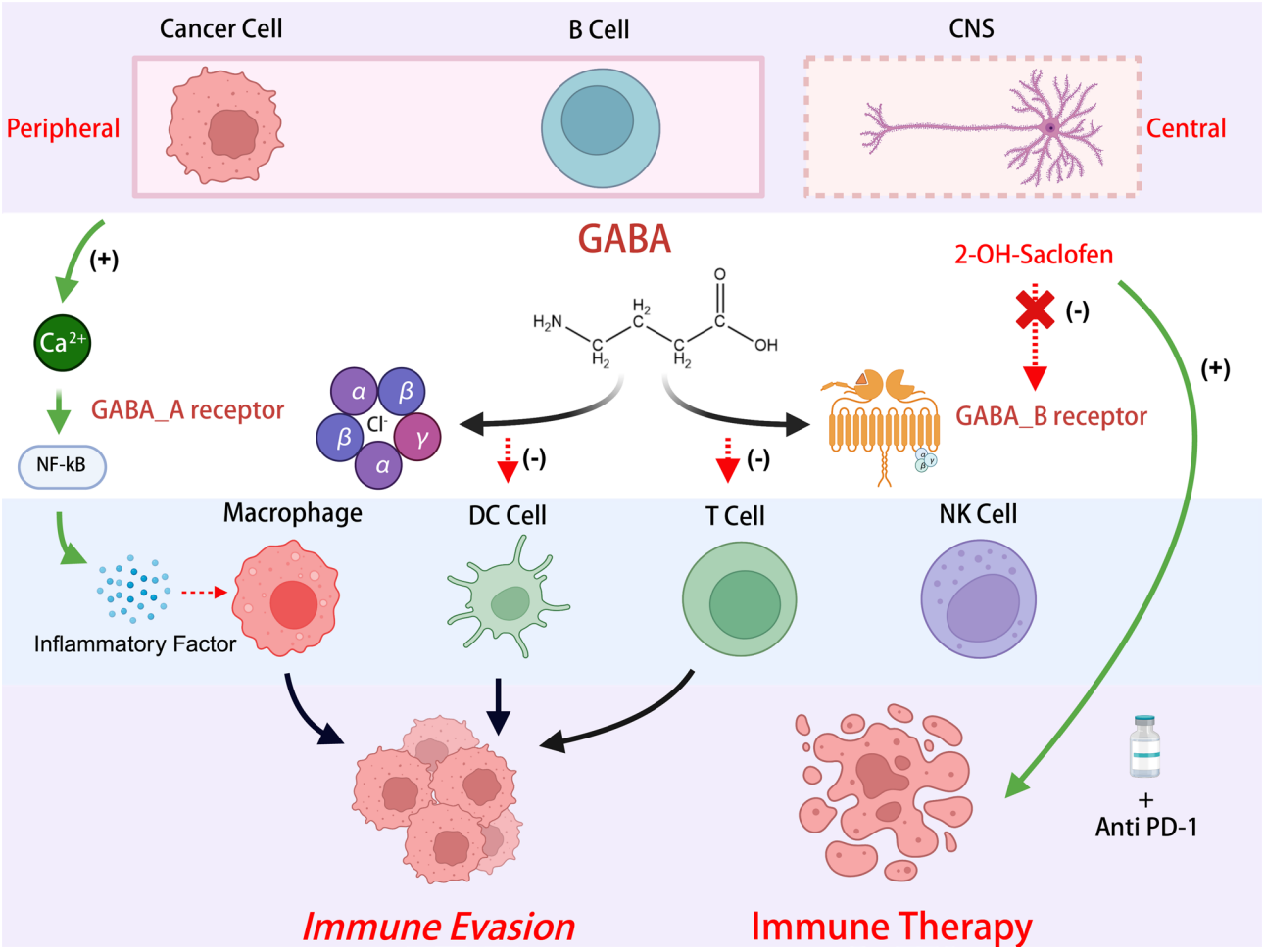


Fig. 9 Role of GABA (γ-Aminobutyric Acid) in tumor immune regulation. GABA can be secreted by the central nervous system, as well as tumor cells or B cells. Within the tumor microenvironment, GABA acts through two major receptors—GABA_A and GABA_B—to modulate immune responses. By promoting calcium (Ca^{2+}) influx, GABA activates the NF-κB signaling pathway, inducing the secretion of inflammatory cytokines. This signaling axis enhances the activity of immunosuppressive cells, such as tumor-associated macrophages and tolerogenic dendritic cells, while inhibiting the cytotoxic functions of T cells and NK cells, thereby promoting immune evasion. The use of GABA_B receptor antagonists (e.g., 2-OH-Saclofen) can block this pathway, reduce immune suppression, and potentially improve the efficacy of tumor immunotherapy

or their downstream signaling components. Although no GABA-related drugs have yet been approved for cancer therapy, existing evidence suggests that many GABAergic drugs—shown to have immunomodulatory potential in other disease models—have demonstrated good safety profiles in clinical use, indicating their potential applicability in the treatment of various solid tumors [224–226].

Hormone-mediated systemic immune modulation

Hypothalamic-pituitary-adrenal axis

Among these, the hypothalamic-pituitary-adrenal (HPA) axis is the central regulatory pathway of stress response. When the body is under stress, this axis is activated, leading to the secretion of glucocorticoids (e.g., cortisol). Elevated glucocorticoid levels in both circulation and the TME can act on various immune cells via nuclear receptors (glucocorticoid receptor, GR) or membrane receptors (e.g., GPR97), inducing widespread transcriptional reprogramming and signaling alterations. These changes affect the survival, differentiation, migration, metabolism, and effector functions of immune cells [100, 227, 228] (Fig. 10). In DCs, glucocorticoids can downregulate pro-inflammatory cytokines (IL-12, IL-6, TNF) and co-stimulatory molecules (CD86, CD80), while inhibiting type I interferon responses and upregulating immunosuppressive cytokines (e.g., IL-10), thereby conferring tolerogenic properties to DCs [97, 98]. Stress-induced GR signaling can promote the expression of TSC22 domain family protein 3 (Tsc22d3), which further suppresses type I IFN pathways and MHC I/II antigen presentation, weakening antitumor immune responses [136]. Furthermore, glucocorticoids can trigger a caspase-independent apoptosis program in DCs by downregulating anti-apoptotic molecules [229]. In T cells, glucocorticoids induce

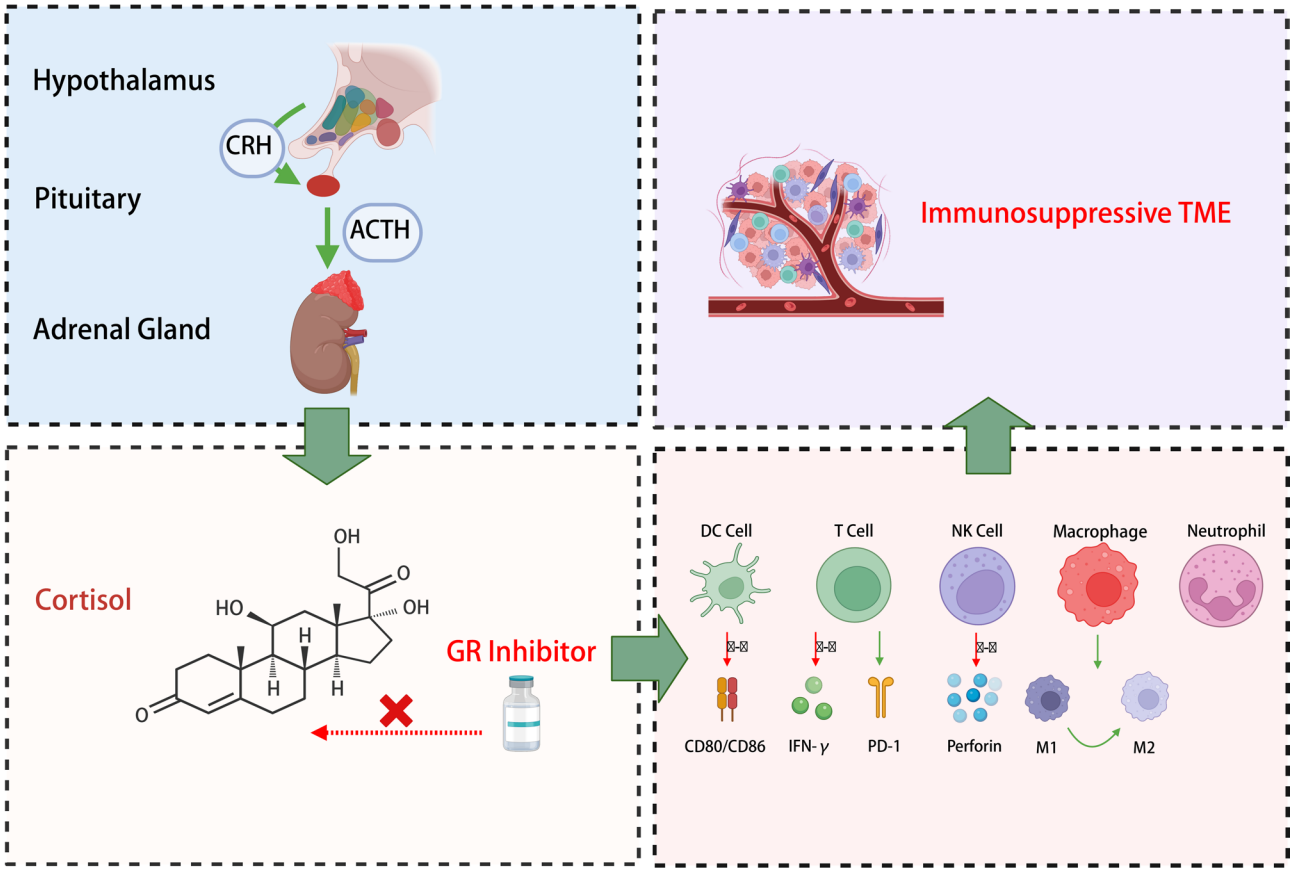


Fig. 10 Immunosuppressive mechanism of the hypothalamic-pituitary-adrenal (HPA) axis via cortisol in the tumor immune microenvironment. Under stress or physiological stimuli, the hypothalamus secretes CRH → pituitary releases ACTH → adrenal cortex produces cortisol. Cortisol signals through the glucocorticoid receptor (GR) to regulate immune cells: it suppresses CD80/CD86 expression on dendritic cells, reduces T cell IFN-γ secretion while upregulating PD-1, inhibits NK cell perforin release, shifts macrophages from M1 to M2, and prolongs neutrophil survival, collectively promoting immunosuppression. GR inhibitors can block this signaling

the expression of pro-apoptotic protein Bim, activating Bak1 and Bax to initiate mitochondrial-dependent intrinsic apoptosis pathways [99]. The hormone–GR complex can translocate to mitochondria, disrupting membrane structure to enhance apoptosis [230]. Glucocorticoids also rapidly inhibit TCR signaling by blocking recruitment and activation of FYN and LCK, and disrupting phosphorylation of downstream molecules [100, 101]. GR activation also upregulates multiple immunosuppressive genes (e.g., Tsc22d3, Dusp1, Nfkbia) and immune checkpoint molecules (e.g., Lag3, Ctla4, Pdcd1), while downregulating chemokines, cytokines, and co-stimulatory molecules, comprehensively suppressing T cell effector functions [102]. GR can also modulate transcriptional and epigenetic landscapes to facilitate the development of memory precursor T cells and Tregs, while strongly inhibiting Th1 cell development and cytotoxic T lymphocyte formation, primarily through upregulation of TCF1 [102, 103]. In TAMs, glucocorticoids suppress the level of "eat me" signal receptor Lrp1 and upregulate "don't eat me" receptor Sirpa via GR-mediated trans-repression, impairing phagocytic tumor clearance [104]. Glucocorticoids also promote TAM polarization toward an immunosuppressive M2-like phenotype, while inhibiting proinflammatory cytokines (e.g., IL-1β, TNF, IL-6) [231]. In MDSCs, GR signaling enhances immunosuppressive activity by downregulating HIF-1α, glycolysis-related genes (e.g., Glut1, Eno1, Mct4), and inflammatory mediators (e.g., Tnf, Il1b) [105, 232]. In NK cells, glucocorticoids suppress cytotoxicity by reducing histone acetylation at promoter/enhancer regions of PRF, GZMB, and IFNγ, and upregulate immune checkpoint PD-1, limiting IFNγ production [106, 233]. In neutrophils, glucocorticoids promote bone marrow egress by downregulating endothelial adhesion molecules (ICAM-1, PECAM-1, VCAM-1) [107], reduce inflammatory site accumulation by upregulating Annexin A1 and downregulating L-selectin [108, 109], and enhance survival via upregulation of anti-apoptotic factors MCL1 and XIAP through activation of p38 MAPK and PI3K pathways [110]. Thus, the HPA axis exerts a broadly immunosuppressive effect via glucocorticoids.

Hypothalamic-pituitary-gonadal axis

The hypothalamic-pituitary-gonadal (HPG) axis regulates immunity through sex hormones and exhibits significant sex-related differences in antitumor immune responses (Fig. 11). Studies have shown that sex influences the efficacy of ICIs in advanced cancer. A meta-analysis of 20 randomized controlled trials comparing anti-PD-(L)1 or anti-CTLA-4 monotherapy with standard treatments found that 19 trials reported greater survival benefit in males, independent of ICI type, histology, or treatment line [234]. Even after adjusting for TMB, PD-L1 expression, and cytokine profiles in the TME, sex remained an independent predictive factor for ICI efficacy [235]. However, this sex-based difference is not consistent. For instance, in a meta-analysis of ICIs plus chemotherapy vs. chemotherapy alone in advanced NSCLC, females derived greater survival benefit from combination therapy than males [236]. This complex difference likely stems from interactions among genetic, hormonal, behavioral, and environmental factors, with sex hormones considered key modulators [237]. Androgen receptor (AR) exerts immunosuppressive effects in the TIME. In prostate cancer patients, AR blockade enhances intratumoral T cell infiltration and induces oligoclonal functional T cell responses [238–240]. AR inhibits its $CD8^+$ T cell cytotoxicity by repressing expression of key effector genes such as GZMB and IFNγ, whose open chromatin regions contain androgen response elements (AREs) [111]. AR also promotes the exhausted T cell phenotype (Tpe) and impairs stem-like properties of $CD8^+$ T

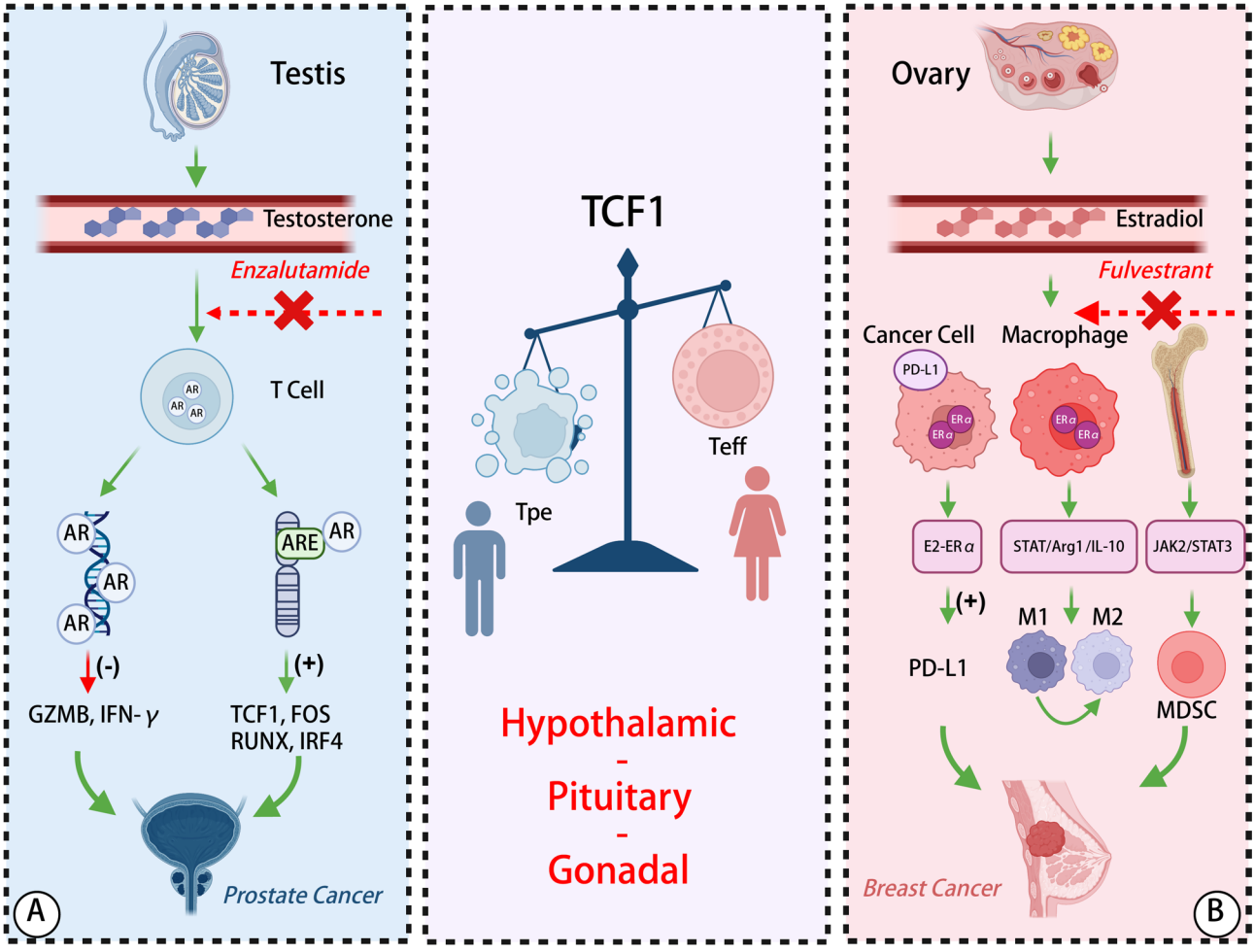


Fig. 11 Role of the hypothalamic-pituitary-gonadal (HPG) axis and sex hormone regulation in tumor immunity. Sex hormones modulate tumor immunity and contribute to gender-based differences by regulating T cells and immunosuppressive cells. Male $CD8^+$ T cells are more likely to maintain TCF1 expression and differentiate into progenitor exhausted T cells (Tpex), whereas female T cells tend to differentiate into effector T cells (Teff). (**A**). Testosterone, through the androgen receptor (AR), regulates T cell gene expression by suppressing GZMB and IFN-γ, while activating TCF1, FOS, RUNX, and IRF4, enhancing the Tpex phenotype. The AR antagonist Enzalutamide can block this pathway. (**B**). Estradiol (E2), via ERα, upregulates PD-L1 expression on tumor cells and activates the STAT/Arg1/IL-10 and JAK2/STAT3 pathways, promoting the accumulation of M2 macrophages and myeloid-derived suppressor cells (MDSCs), thus enhancing immune suppression. The ER antagonist Fulvestrant can reverse these pathways and improve the immune microenvironment

cells through epigenetic remodeling and increased accessibility to transcription factor targets (e.g., FOS, RUNX, IRF4) [112]. In bladder cancer, male CD8⁺ T cells more readily maintain TCF1 expression and develop a Tpe phenotype, while female T cells tend to differentiate into Teff [113]. AR directly promotes TCF1 expression and related epigenetic programs to drive Tpe formation [113] (Fig. 11A). In contrast, estrogens and estrogen receptors also play important roles in shaping the TIME. In NSCLC cell lines and PDX models, tumor cells upregulate PD-L1 via an autocrine E2–ERα axis, promoting an immunosuppressive TIME. This effect is particularly evident in EGFR-mutant NSCLC and can be reversed by inhibiting EGFR–ERK1/2–AKT signaling [114]. Estrogens also promote M2 polarization of TAMs, impair CD8⁺ T cell function, and contribute to ICI resistance [115, 116]. Blocking ERα signaling (e.g., with fulvestrant) restores T cell function and enhances ICI efficacy. Similar findings were validated in smoking-induced lung cancer models, where aromatase inhibitors combined with NSAIDs showed synergistic antitumor effects [117, 118]. Estrogens also regulate MDSCs, which are elevated in various tumors. In glioblastoma (GBM) models, sex-specific MDSC subtypes mediate immune suppression: males are enriched with monocytic MDSCs, while females have more granulocytic MDSCs [241, 242]. ERα promotes MDSC differentiation and function via JAK2–STAT3 signaling, confirmed across multiple tumor models [119]. Liver metastasis-associated ICI resistance is also linked to MDSC and TAM enrichment. Recent studies show that estrogens promote MDSC recruitment in hepatic metastases via TNFα signaling, thereby suppressing T cell–mediated responses [243–245]. Oophorectomy or ER inhibition can reverse this process and improve ICI efficacy [245] (Fig. 11B). Overall, sex hormones directly and indirectly shape the TIME and influence immunotherapy outcomes. Both androgens and estrogens represent potential immunotherapeutic targets, though their precise roles across tumor types and treatments warrant further investigation.

Hypothalamic-pituitary-thyroid axis

The hypothalamic-pituitary-thyroid (HPT) axis regulates immune cell function and differentiation by controlling the secretion of thyroid hormones (triiodothyronine [T3] and thyroxine [T4]). Recent studies highlight the role of the TSH/TSHR signaling in tumor immune evasion, especially in CRC. TSH receptor (TSHR) is highly expressed in CRC tumor cells and CD8⁺ T cells and has been identified as a key intrinsic driver of T cell exhaustion (Fig. 12). Conditional deletion of TSHR in tumor-infiltrating CD8⁺ T cells enhances effector differentiation and suppresses PD-1 and TIM3 expression via the PKA/cAMP/CREB pathway, improving immune responses. CRC cells can secrete TSHR via exosomes, increasing TSHR expression in CD8⁺ T cells and promoting immunosuppression

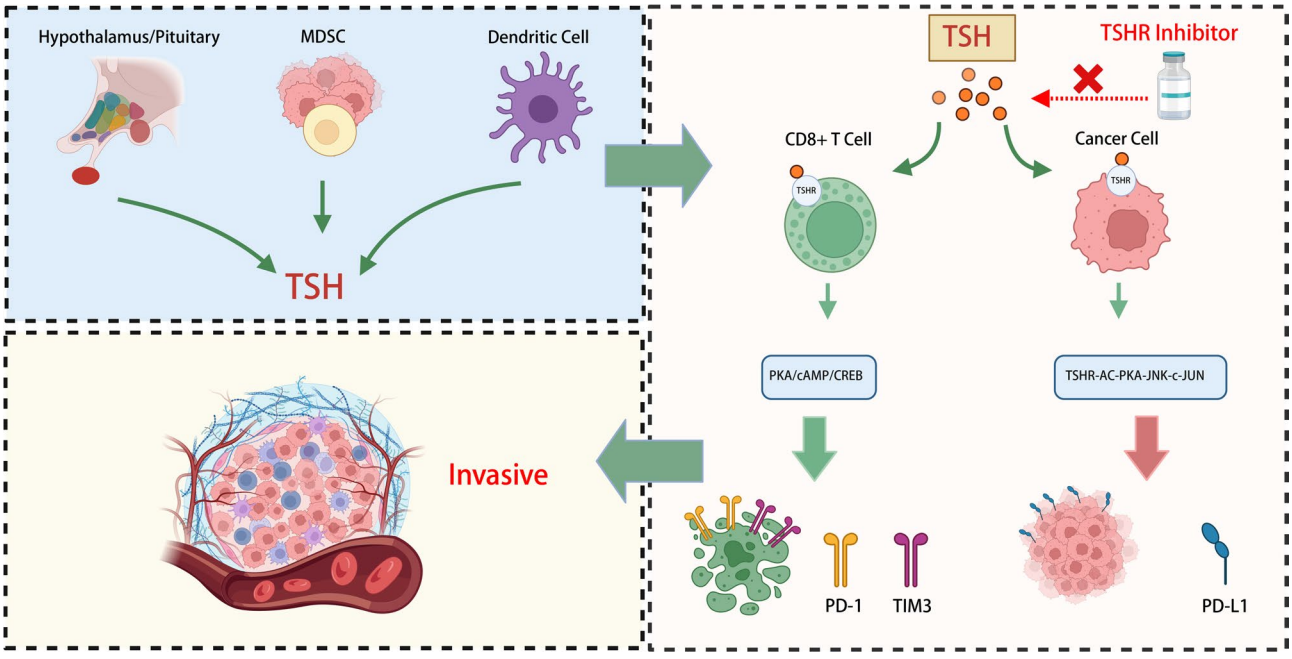


Fig. 12 Mechanism by which TSH promotes tumor invasion and immune evasion through its receptor-mediated signaling. Thyroid-stimulating hormone (TSH) can be secreted by the pituitary, tumor cells, MDSCs, and dendritic cells, and acts on cancer and immune cells via the circulatory system. TSH binds to TSH receptors (TSHR) on CD8⁺ T cells, activating the PKA/cAMP/CREB pathway, which induces expression of immune checkpoint receptors such as PD-1 and TIM-3, promoting immune evasion. TSH binding to TSHR on tumor cells activates the TSHR–AC–PKA–JNK–c-JUN pathway, enhancing cancer cell proliferation and invasiveness. TSHR inhibitors can block this signaling and suppress the pro-tumor effects mediated by TSH

in the TME. MDSCs are considered the primary source of TSH in the TME and influence immune cell function through TSH secretion. CRC tumors with low TSHR expression exhibit better responses to immunotherapy, suggesting TSHR as a potential biomarker [120]. During immune evasion, monocyte-derived dendritic cells (moDCs) are the main source of TSH in the TME. TSH secreted by moDCs promotes proliferation and invasion in high-TSHR-expressing tumors (e.g., thyroid cancer, glioma) via the TSHR–AC–PKA–JNK–c-JUN pathway. TSH also induces PD-L1 expression in tumor cells, inhibiting T cell activation. Inhibiting TSHR reduces PD-L1 levels in tumor and myeloid cells and enhances effector T cell activation, reversing immune escape [121].

Melatonin

Additionally, melatonin (MLT), an endogenous hormone secreted by the pineal gland, has shown potential to enhance T cell function and increase sensitivity to immunotherapy (Fig. 13). Studies demonstrate that MLT boosts NK cell activity activated by local radiofrequency ablation (RFA) and exerts synergistic antitumor effects when combined with RFA. It can also reverse the Warburg effect, lowering tumor malignancy [122]. MLT induces tumor-associated neutrophils (TANs) to polarize toward N1 antitumor phenotype, enhances neutrophil extracellular trap (NET) formation, and induces tumor cell apoptosis via direct cell–cell contact [123]. In KRAS-mutant NSCLC, MLT improves the immunosuppressive TME by downregulating PD-L1 by inhibition of the YAP pathway [124]. In HNSCC, MLT inhibits ERK1/2–FOSL1 signaling, blocking EMT and reducing PD-L1 levels [125]. In HCC, MLT shows both direct anticancer activity and immune enhancement by suppressing PD-L1 and its upstream regulator HIF-1α, while increasing expression of JNK, P38, and their phosphorylated forms [126]. In gastric cancer, MLT promotes $CD8^+$ T cell recruitment to tumors via exosome-mediated mechanisms and enhances macrophage secretion of TNF-α and CXCL10, thereby amplifying immune responses [127]。 .

Regulation of neural signaling by the immune system and tumors

The nervous system plays a regulatory role in immune responses during infection and inflammation [246]. Conversely, the immune system can also modulate nervous system function by releasing various signaling molecules, even influencing the growth and extension of nerve fibers. In certain cases, these changes may permeate into tumor tissues [231, 247]. During inflammatory responses, leukocyte infiltration is accompanied by the release of pain-associated mediators, which induce neuroplastic changes and promote peripheral nerve remodeling [248]. For example, neurotrophic factors such as NGF and BDNF, secreted by macrophages, mast cells, and other immune cells, may drive an "axonogenic switch" process in tumor innervation. This mechanism resembles neural remodeling observed in inflammatory

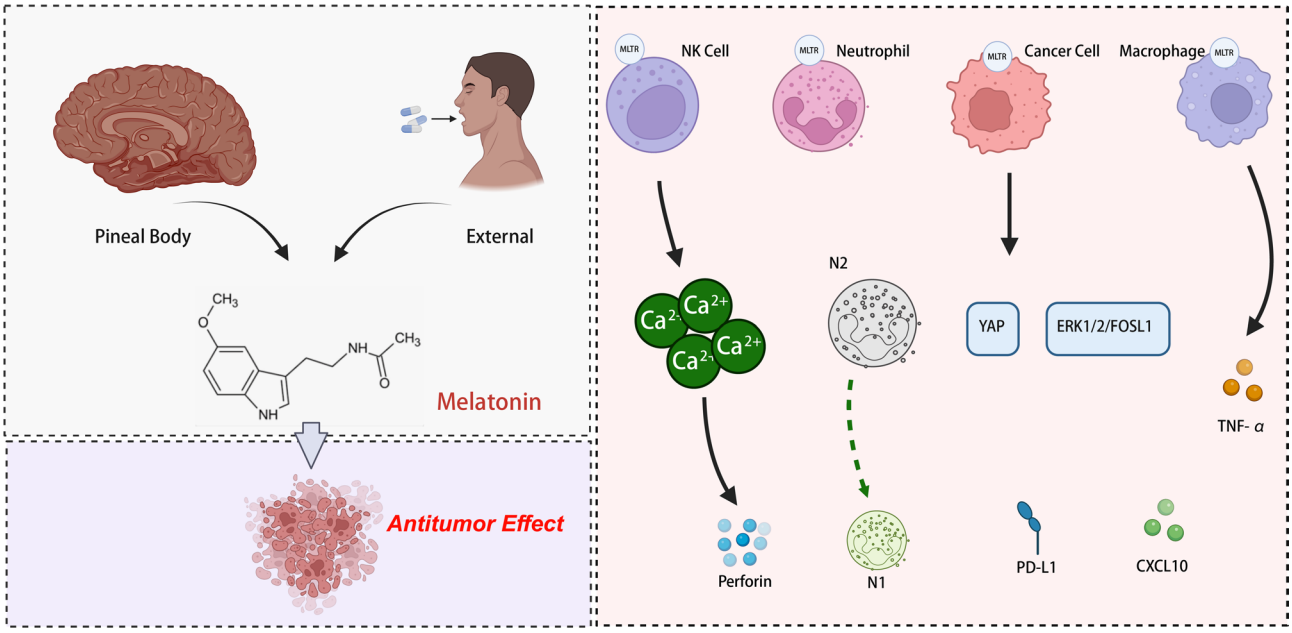


Fig. 13 Mechanism of melatonin in regulating anti-tumor immunity. Melatonin, secreted by the pineal gland or supplied exogenously, exerts multiple immunoregulatory effects by acting on melatonin receptors (MLTR) expressed on immune and tumor cells. Specifically, melatonin enhances calcium signaling activation in NK cells, promoting the release of cytotoxic molecules. It induces tumor-associated neutrophils (TANs) to transition toward the anti-tumor N1 phenotype. It increases macrophage secretion of TNF-α and CXCL10. It inhibits YAP and ERK1/2-FOSL1 signaling in tumor cells, reducing PD-L1 expression and boosting anti-tumor immune responses

pain and may promote tumor-associated neurogenesis through recruitment of brain-derived neural precursor cells [248, 249]. In murine models of rheumatoid inflammation, macrophage activation is associated with significantly enhanced sensory and sympathetic innervation as well as angiogenesis [250]. Various immune cells—including macrophages, neutrophils, T lymphocytes, and mast cells—have been found to express NGF and BDNF [249, 251, 252]. Moreover, in the context of nerve injury, IL-1β secreted by macrophages can induce NGF synthesis in non-neuronal cells [231]. Although direct evidence is still lacking to confirm the role of neurotrophic factors secreted by tumor-infiltrating leukocytes in modulating tumor nerve growth and neurogenesis, mechanistic insights suggest this is a plausible scenario [253].

The crosstalk linking peripheral tumors with the nervous system is defined by mutual bidirectional communication. Although autonomic neural signals modulate tumor cells and the surrounding immune microenvironment, tumor cells actively manipulate neural signaling to promote their survival, thereby reinforcing tumor–nervous system interdependence. For instance, in mouse models of pancreatic ductal adenocarcinoma, cancer cells secrete NGF, which promotes the growth of sympathetic nerve within the tumor microenvironment, thereby facilitating immune escape [254]. Likewise, tumor cells originating from human prostate, colorectal, and pancreatic cancers are capable of producing precursor forms of brain-derived neurotrophic factor, which attract autonomic innervation and promote tumor progression [255]. Recent advances in cancer neuroscience have revealed that, despite anatomical or mutational differences among tumor types, they may share common mechanisms that activate specific brain neural circuits—particularly in the hypothalamus or brainstem—which govern autonomic signals transmitted to peripheral organs. Through these circuits, tumors establish functional communication with peripheral organs. The earliest characterized instance of a tumor-induced neural circuit shows that multiple murine tumor types (e.g., pancreatic ductal adenocarcinoma and colorectal adenocarcinoma) can activate catecholaminergic neurons in the rostral ventrolateral medulla (RVLM), a key upstream region of sympathetic output. Activation of this region promotes tumor growth by suppressing $CD8^+$ T cell function [256]. Notably, these tumor-induced central neuro-immune mechanisms may themselves be regulated by hormones or autonomic signaling within the tumor. For example, murine lung cancer, colorectal adenocarcinoma, fibrosarcoma, and melanoma can activate hypothalamic neurons, leading to pituitary secretion of α-melanocyte-stimulating hormone (α-MSH). This α-MSH, induced by tumors, promotes the generation of MDSCs in the bone marrow, thereby inhibiting the host's antitumor immune response [257]. Conversely, recent research has shown that various types of murine peripheral tumors frequently secrete galectin-3 and leukemia inhibitory factor, which can also be detectable in the plasma of certain patients with solid tumors. These tumor-secreted signals act synergistically to stimulate the paraventricular nucleus (PVN) of the hypothalamus, thereby enhancing local sympathetic innervation of tumors, contributing to the establishment of an immunosuppressive TME [29]. Therefore, disrupting the interactions among the nervous, immune, and tumor systems may open new therapeutic avenues for the treatment of various peripheral tumors. Currently, antagonists targeting LIF or GAL3 have achieved preliminary success in clinical trials, demonstrating potential antitumor efficacy [258–261].

Emerging cancer therapies targeting the neuro-immune axis

ICIs in combination with neuromodulation tumor denervation

Immune checkpoint molecules are considered one of the primary mechanisms by which cancers evade immune surveillance. Notably, molecules such as PD-1 and its ligand PD-L1 can be expressed on tumor-associated nerves within the TME, leading to T cell functional suppression and promoting tumor progression [262]. Therapeutic strategies directed at these molecules seek to boost antitumor immune responses within the TME, thereby inhibiting tumor development and even inducing tumor regression [262–265]. ICIs targeting these molecules restore the ability of immune cells to recognize and kill tumor cells by blocking checkpoint pathways, and have significantly improved clinical outcomes in various malignancies. However, only a subset of patients achieve durable clinical responses, indicating that inhibitory mechanisms within the TME still limit ICI efficacy [266, 267]. Recent studies have shown that the nervous system can influence antitumor immune responses by modulating immune cell activation, exhaustion, and checkpoint molecule expression, making the neuro–immune–tumor axis a potential regulator of ICI sensitivity. For example, in prostate cancer tissue, the density of $PD\text{-}L1^+$ nerve fibers is negatively correlated with $CD8^+$ tumor-infiltrating lymphocyte (TIL) levels and serves as an independent prognostic indicator for recurrence-free survival [262].

Interventions targeting sympathetic nerve activity have been shown to enhance ICI efficacy. In animal models, temperature regulation, β-adrenergic blockade, or ADRB2 knockout reduced PD-1 expression and promoted $CD8^+$ effector T cell accumulation in the TME, thereby enhancing anti–PD-1 efficacy [268]. In a preclinical study of fibrosarcoma and colorectal cancer in mice, the combination of propranolol (a non-selective β-blocker) with anti–CTLA-4 antibody increased T cell

infiltration and reduced MDSCs, significantly improving anti–CTLA-4 therapy outcomes [137]. Another clinical study in patients with metastatic melanoma showed that concurrent treatment with immunotherapy and non-selective β-blockers significantly improved overall survival [269]. In a phase Ib/II clinical trial (NCT03384836), the combination of propranolol and pembrolizumab achieved an initial objective response rate of 78%, accompanied by increased IFN-γ and decreased IL-6 levels [270]. However, a subsequent phase III trial (NCT02362594) did not observe recurrence-free survival benefits in a high-risk population [271], suggesting that the benefit may be population-specific. Furthermore, β-blockers can synergize with radiotherapy, reversing adrenergic suppression of abscopal antitumor effects, enhancing $CD8^+$ T cell migration, and reducing the accumulation of M2 macrophages and Treg cells [272–274]. Beyond adrenergic pathways, the voltage-gated sodium channel Nav1.8 may also participate in regulating neuro–immune interactions within the TME. The sodium channel blocker lidocaine has been found to possess immunomodulatory and antitumor potential [275, 276]. Intraoperative use in breast cancer can reduce expression of MMP3, NETs-related markers, and MPO, potentially suppressing postoperative tumor recurrence mechanistically [277]. In summary, neural modulation can enhance ICI-mediated antitumor immune responses through multiple pathways, representing a promising strategy to improve immunotherapy efficacy. However, the optimal dose, timing, and combination regimen require further clinical validation. Given the substantial interindividual heterogeneity in neural activity, biomarkers reflecting neuro–immune status are urgently needed to identify patients most likely to benefit.

Repurposing neuroactive drugs

The repurposing of neuroactive drugs offers novel opportunities for cancer therapy. Current studies have explored multiple agents targeting diverse neural pathways (Table 3). Among them, the β-AR antagonist propranolol has been most extensively investigated, with phase I–III clinical trials conducted in ovarian, colorectal, gastric, esophageal, breast, triple-negative breast, pancreatic, melanoma, bladder, prostate, soft tissue sarcoma, Kaposi sarcoma, and non-small cell lung cancers. Cholinergic modulators such as donepezil and bethanechol have been evaluated in breast, small cell lung, head and neck, and pancreatic cancers, with some trials already completed. The voltage-gated sodium channel blocker lidocaine has also been tested across breast, lung, pancreatic, ovarian, and colorectal cancers, including several phase II–IV studies. In addition, dopamine receptor antagonists ONC201/ONC101 are undergoing clinical assessment in acute myeloid leukemia, neuroendocrine tumors, endometrial cancer, and ovarian cancers. SSRIs, including fluoxetine and escitalopram, have also entered clinical trials for colorectal, non-small cell lung, and pancreatic cancers. Although these findings highlight the therapeutic potential of neuroactive drugs in oncology, challenges remain, including limited tumor specificity, risk of adverse effects, and lack of commercial incentives due to expired patents. Nevertheless, with advancing insights into neuro–tumor interactions, such agents may eventually be integrated with chemotherapy, targeted therapy, and immunotherapy, thereby providing new strategies for cancer treatment.

Anti-neurogenesis agents

Tumor-induced neurogenesis and axonal infiltration can promote tumor growth, invasion, and immune evasion, making anti-neurogenesis therapies targeting tumor–nerve interactions an emerging area of research. Studies have shown that Tanezumab inhibits the NGF/TrkA pathway, suppressing the Warburg effect and thereby reducing the neuroinvasive potential of pancreatic cancer cells [278]. Neutralizing antibodies against BDNF and the Trk inhibitor K252a effectively induce apoptosis and inhibit invasion in HepG2 and HCCLM3 cells [279]. COX-2 inhibitors have been reported to significantly suppress adult neurogenesis, while meloxicam inhibits hepatocellular carcinoma progression and enhances immunotherapy sensitivity via the microRNA-200/PD-L1 pathway [280]. Moreover, Netrin-1, a secreted protein initially identified as a chemotactic factor in neural development, guides axonal growth and neural network formation. Treatment with anti–Netrin-1 antibodies (NP137) can inhibit EMT, reduce metastatic burden, and increase tumor cell sensitivity to chemotherapy. In a phase I clinical trial including 14 patients with advanced esophageal cancer, according to RECIST v1.1 criteria, 8 patients achieved stable disease (57.1%) and 1 patient achieved a partial response (7.1%), with target lesions shrinking by 51.16% at 6 weeks and reaching a 54.65% reduction over 6 months [281, 282]. Although these studies demonstrate the potential of anti-tumor neurogenesis interventions to inhibit neural invasion, reduce metastasis, and enhance chemotherapy and immunotherapy sensitivity, neural-related signaling plays important roles in normal physiology. Long-term intervention may cause neurotoxicity or systemic adverse effects, and clinical data remain limited to early-phase, small-sample studies, lacking large-scale, multicenter validation.

miRNA/siRNA-based therapies

RNA interference (RNAi) therapies can specifically silence key molecules within tumor–nerve–immune signaling, thereby intervening in tumor growth. IA-2 (also known as islet cell antigen 512 [ICA512] or receptor-type

Table 3 Neuro-immune–targeted therapeutic agents with cancer relevance

Drug	Target	Cancer type(s)	Stage	References	Status
Propranolol	β-ARs	Ovarian, primary peritoneal, or fallopian tube cancer	Phase 1	NCT01504126	Completed
Propranolol	β-ARs	Ovarian cancer	Phase 1	NCT01308944	Completed
Propranolol	β-ARs	Colorectal cancer	Phase 1	NCT03245554	Unknown status
Propranolol	β-ARs	Colorectal cancer	Phase 3	NCT00888797	Completed
Propranolol	β-ARs	Gastric cancer	Phase 2	NCT04005365	Unknown status
Propranolol	β-ARs	Esophageal adenocarcinoma	Phase 2	NCT04682158	Recruiting
Propranolol	β-ARs	Breast cancer	Phase 2	NCT00502684	Completed
Propranolol	β-ARs	Breast cancer	Phase 2	NCT01847001	Ongoing
Propranolol	β-ARs	Breast cancer	Phase 2	ACTRN12615000889550	Completed
Propranolol	β-ARs	Breast cancer	Phase 2	NCT02596867	NCT02596867
Propranolol	β-ARs	TNBC	Phase 2	NCT05741164	Not yet recruiting
Propranolol	β-ARs	Pancreatic cancer	Phase 2	NCT03838029	Ongoing
Propranolol	β-ARs	Melanoma	Phase 1	NCT03384836	Completed
Propranolol	β-ARs	Melanoma	Phase 3	NCT02962947	Unknown status
Propranolol	β-ARs	Bladder cancer	Phase 2	NCT04848519	Ongoing
Propranolol	β-ARs	Bladder cancer	Phase 2	NCT04493489	Unknown status
Propranolol	β-ARs	Prostate cancer	Phase 2	NCT05679193	Completed
Propranolol	β-ARs	Prostate cancer	Phase 2	NCT01857817	Terminated
Propranolol	β-ARs	Prostate cancer	Phase 2	NCT03152786	Terminated
Propranolol	β-ARs	Soft tissue sarcoma	Phase 2	NCT05961761	Recruiting
Propranolol	β-ARs	Soft tissue sarcoma	Phase 2	NCT03108300	Unknown status
Propranolol	β-ARs	Kaposi sarcoma	Phase 2	NCT06445166	Not yet recruiting
Propranolol	β-ARs	Kaposi sarcoma	Phase 2	NCT05797662	Not yet recruiting
Propranolol	β-ARs	NSCLC	Phase 1	NCT05979818	Not yet recruiting
Donepezil	AChE	Breast cancer	Phase 2	NCT01466270	Completed
Donepezil	AChE	SCLC	Phase 3	NCT00006349	Completed
Donepezil	AChE	Head and neck cancer	Phase 3	NCT00656513	Completed
Donepezil	AChE	Head and neck cancer	Phase 3	NCT00003139	Completed
Donepezil	AChE	Head and neck cancer	Phase 3	NCT00168181	Completed
Donepezil	AChE	Pancreatic cancer	Phase 1	NCT03572283	Active, not recruiting
Bethanechol	mAChRs	Pancreatic cancer	Phase 1	NCT03572283	Ongoing
Bethanechol	mAChRs	Pancreatic cancer	Phase 2	NCT05241249	Recruiting
Lidocaine	VGSC	Breast cancer	Phase 2	NCT02839668	Completed
Lidocaine	VGSC	NSCLC	Not Applicable	ChiCTR2000030629	Ongoing
Lidocaine	VGSC	Pancreatic cancer	Not Applicable	NCT03245346	Recruiting
Lidocaine	VGSC	Pancreatic cancer	Not Applicable	NCT05470166	Completed
Lidocaine	VGSC	Ovarian cancer	Not Applicable	NCT05450055	Not Yet Recruiting
Lidocaine	VGSC	Colorectal cancer	Phase 3	NCT00236249	Completed
Lidocaine	VGSC	Colorectal cancer	Phase 1	NCT02786329	Unknown status
Lidocaine	VGSC	Colorectal cancer	Not Applicable	NCT05250791	Recruiting
Lidocaine	VGSC	Colorectal cancer	Not Applicable	NCT05484687	Completed
Lidocaine	VGSC	Colorectal cancer	Phase 4	NCT01841294	Unknown status
ONC101	DRD2/DRD3 antagonist	Acute myeloid leukaemia	Phase 1	NCT03932643	Ongoing
ONC201	DRD2/DRD3 antagonist	Neuroendocrine tumours	Phase 2	NCT03034200	Ongoing
ONC201	DRD2/DRD3 antagonist	Endometrial cancer	Phase 2	NCT03485729	Ongoing
ONC201	DRD2/DRD3 antagonist	Ovarian, fallopian tube, or primary peritoneal cancer	Phase 2	NCT04055649	Ongoing
Fluoxetine	5-HT	Colorectal cancer	Phase 1	NCT06225011	Recruiting
Fluoxetine	5-HT	NSCLC	Phase 2	NCT00005850	Completed
Escitalopram	5-HT	Pancreatic cancer	Phase 2	NCT05289830	Terminated

protein tyrosine phosphatase [PTPRN]) is an integrative transmembrane protein of dense core vesicles (DCVs) involved in the secretion of insulin, gonadotropins, and neurotransmitters such as NE, dopamine, and ACh [283, 284]. In SCLC, RNAi-mediated knockdown of IA-2 or transfection with a miR-342 mimic significantly reduces tumor cell–autocrine ACh levels, thereby inhibiting SCLC proliferation [285]. Similarly, in ovarian cancer, DUSP1 has been identified as a key mediator of NE-induced resistance to paclitaxel- and cisplatin-induced apoptosis. In vivo experiments demonstrate that RNAi silencing of DUSP1 not only markedly enhances paclitaxel's antitumor efficacy but also significantly increases tumor cell apoptosis [286]. NGF can upregulate miR-21-5p levels in tumor-derived exosomes, and inhibition of miR-21-5p can reverse NGF-mediated promotion of perineural invasion (PNI) in pancreatic cancer Mia-PaCa-2 cells [278]. However, clinical application of RNAi faces multiple challenges, including low delivery efficiency, poor in vivo nucleic acid stability, and potential off-target immune activation. To overcome these limitations, researchers are developing novel targeted nanoparticle carriers, local delivery strategies, and controlled-release systems to enhance tissue specificity and prolong the therapeutic effect of RNAi molecules. These innovative approaches are expected to facilitate the translation of RNAi from bench to bedside, providing a feasible strategy for precise intervention in the tumor–nerve–immune network.

Tumor denervation

Tumor denervation, through physical or chemical methods, blocks pro-tumorigenic and immunosuppressive neural signals, thereby modulating the TME and enhancing antitumor immune responses. PNI, the infiltration of tumors around nerves, is a common feature of PDAC and is closely associated with impaired immune function, characterized by reduced $CD8^+$ T cells and Th1 cells, alongside an increased proportion of Th2 cells. In tumor-bearing mouse models, bilateral subdiaphragmatic vagotomy to disrupt PNI significantly increases tumor-infiltrating $CD8^+$ T cells, elevates the Th1/Th2 ratio, and improves survival [287]. Studies in Apc^(Min/+) mice further indicate that peripheral innervation of the small intestine plays a key regulatory role in tumor development. Notably, disruption of vagal innervation, rather than sympathetic denervation, effectively suppresses tumor growth [288]. Chemical denervation also demonstrates antitumor potential. For instance, benzalkonium chloride (BAC) treatment of rat stomachs significantly reduces the number of myenteric neurons, increases gastric mucosal area, and decreases both the incidence and volume of adenocarcinoma, with more pronounced effects when combined with pyloroplasty [289]. Moreover, botulinum toxin type A1 (BoNT/A1) inhibits cholinergic neural signaling. When combined with anti-PD-1 immunotherapy, BoNT/A1 reduces the proportion of MDSCs, counteracts the increase in Tregs, and promotes greater infiltration of $CD4^+$ and $CD8^+$ T cells into the TME, thereby significantly enhancing therapeutic efficacy [290]. Neural fibers can also be disrupted by radiofrequency, electromagnetic, or chemical methods; however, current research primarily focuses on pain relief rather than direct tumor treatment [291]. Although denervation shows substantial antitumor potential in experimental models, its clinical translation faces several challenges. These include insufficient targeting specificity, which may impair normal neural function, uncertain long-term safety, heterogeneity among tumor types affecting efficacy, and the complexity of the immune microenvironment increasing uncertainty in immune modulation. These factors currently limit the widespread clinical application of tumor denervation strategies.

Cell therapy

Cell therapy has shown great potential in tumor control and neural regulation, with TRKB, a key member of the oncogenic TRK family, emerging as an increasingly important target. TRKB is a transmembrane protein located on the surface of neural cells and is often considered a marker of tumor malignancy, being overexpressed in various cancers. TRKB overexpression is typically activated by its ligand BDNF, which subsequently triggers downstream signaling pathways such as PI3K and Akt, promoting tumor cell proliferation, invasion, and metastasis while inhibiting apoptosis and preventing abnormal growth. Moreover, aberrant TRKB expression is closely associated with the development of tumor drug resistance [279, 292, 293]. Studies have shown that TRKB inhibitors can effectively reduce tumor growth, invasion, and distant metastasis [294–296]. Unlike broad-spectrum therapies targeting the entire TRK family, recent research has successfully developed TRKB-specific CAR-T cells. Both BDNF-CAR T and NTF4-CAR T have demonstrated efficacy in hepatocellular carcinoma and pancreatic cancer models [297]. These CAR-T cells exhibit dose-dependent cytotoxicity against tumor cell lines with high TRKB expression, accompanied by elevated cytokine release. Furthermore, transfection-induced TRKB overexpression in low-expressing cell lines significantly enhances their susceptibility to CAR-T killing, indicating TRKB-dependent cytotoxicity. In murine hepatocellular carcinoma xenograft models, NTF4-CAR T significantly suppresses tumor growth, whereas BDNF-CAR T shows limited efficacy, likely due to PD-L1 upregulation in the tumor microenvironment causing CAR-T functional inhibition [298]. Future strategies aim to enhance BDNF-CAR T efficacy through combination therapy with PD-L1

inhibitors. Another potential challenge for TRKB-targeted CAR-T immunotherapy is "on-target, off-tumor" toxicity. Notably, the affinity between BDNF-CAR T or NTF4-CAR T and their natural ligand receptor is lower than that of typical antigen–antibody interactions, which may reduce off-target risks [299–301]. Experiments indicate that both CAR-T types do not affect T cell proliferation and show no significant toxicity toward low- or non-TRKB-expressing tumor cells and normal cells. Public database analyses indicate high amino acid homology of TRKB and its ligands BDNF and NTF4 between humans and mice (92%, 100%, and 100%, respectively), supporting translational relevance and efficacy in animal models. Importantly, administration of BDNF-CAR T or NTF4-CAR T in tumor-bearing mice did not affect body weight, food intake, or behavioral activity, indicating good safety profiles [297]. Given the rapid advancement of CAR-T technology, potential safety concerns—including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and severe off-target effects—may be mitigated in the future by incorporating suicide genes or safety switches into CAR constructs, providing more reliable protection during therapy [302].

Oncolytic virus therapy

Oncolytic viruses (OVs) selectively infect and lyse tumor cells while simultaneously activating antitumor immune responses. Neural stem cells (NSCs) are multipotent progenitors capable of differentiating into neurons, astrocytes, and oligodendrocytes, and they persist in specific regions of the adult brain. Leveraging their intrinsic tumor-tropic properties, NSCs have been developed as delivery vehicles for OVs, primarily for treating malignant brain tumors. The FDA-approved immortalized NSC line, HB1.F3.CD21, has been extensively utilized in glioma gene therapy and OV studies, with validation in multiple preclinical and clinical trials [303]. CRAd-S-pk7 is an oncolytic adenovirus (oAd) engineered for glioma treatment, with modifications including the Survivin promoter and pk7 fiber, enhancing tumor selectivity. The HB1.F3.CD21 cell line supports CRAd-S-pk7 replication, and at high viral doses, cell lysis occurs around days 2–3 in culture [304]. In orthotopic glioma models, intracranial injection of NSCs carrying CRAd-S-pk7 significantly prolongs survival in mice, demonstrating superior efficacy compared to virus alone [304–306]. This strategy has advanced to clinical evaluation. In a trial including 11 patients with glioblastoma and 1 patient with anaplastic astrocytoma, NSCs loaded with CRAd-S-pk7 were administered to the post-surgical resection cavity in combination with standard chemotherapy. No dose-limiting toxicities were observed, and only one case of viral meningitis occurred due to inadvertent injection into the lateral ventricle. Although progression-free survival and overall survival did not reach statistical significance, both metrics were slightly higher than historical controls [307].

This combinatorial approach has also been explored in ovarian cancer. Intraperitoneal injection of NSCs infected with CRAd-S-pk7 slowed orthotopic ovarian tumor growth (OVCAR8 and ID8) while avoiding neutralization by circulating antibodies; the antitumor effect was further enhanced when combined with cisplatin [308]. Both endogenous and ex vivo expanded NSCs, including the HB1.F3.CD21 line, exhibit pronounced tumor-tropic behavior [309, 310]. In murine models, NSCs implanted in the contralateral hemisphere can migrate across the brain midline to reach tumor sites. Notably, CRAd-S-pk7 modifications can further enhance NSC tumor homing via upregulation of CXCR4 and VEGFR2 [305]. Extensive studies have demonstrated that even without viral cargo, NSCs administered intravenously can actively migrate to tumors, such as liver and skeletal micrometastases of neuroblastoma [311, 312], or as carriers for antibodies targeting orthotopic breast tumors [313]. In ovarian cancer models, however, intraperitoneal administration is more effective than intravenous injection for NSC tumor distribution [314]. While NSCs delivered intravenously tend to become trapped in peripheral tissues [315], their ability to traverse pulmonary capillaries is approximately twice that of mesenchymal stem cells (MSCs) [316]; nevertheless, their larger cell size still limits intravenous delivery efficiency. Future research should focus on enhancing NSC tumor-specific targeting and achieving controlled expression of therapeutic cargoes to accelerate clinical translation.

Behavioral regulation

Stress represents the physiological and emotional responses experienced by individuals when facing life challenges and is regulated by the nervous system. Stress reduction through physical activity and mindfulness- or cognitive-behavior-based interventions—such as yoga, tai chi, or meditation—has been shown to induce multiple immunological changes, including decreased inflammation, enhanced Th1 cell responses, and increased NK cell activity [317]. Psychological interventions implemented in patients with non-metastatic breast cancer prior to surgery and adjuvant therapy can significantly reduce the risk of death or recurrence [318], while also improving quality of life and subjective well-being [319]. In liver cancer studies, eustress (positive stress) enhances the sensitivity of mice to immunotherapy. Mechanistically, eustress activates the peripheral sympathetic nervous system, increasing NE and EPI levels in serum and tumor tissue. Elevated NE and EPI subsequently activate β-AR signaling in tumor cells and tumor-infiltrating

myeloid cells. Activation of β-ARs directly downregulates CCL2 expression in tumor and immune cells, reducing the infiltration of TAMs and MDSCs in the tumor microenvironment, while enhancing $CD8^+$ T cell infiltration and function, ultimately increasing sensitivity to (ICIs such as anti–PD-L1 therapy [320]. Furthermore, certain psychotropic drugs may exhibit immunostimulatory effects, for example by modulating lymphocyte activity within tumors. In patients with triple-negative breast cancer, the use of psychotropic inhibitors or stimulants is associated with higher rates of pathological complete response [321]. These studies indicate that stress management exerts multifaceted effects on immune function and may significantly enhance cancer treatment outcomes. Future research should clarify the specific immune cell subpopulations and receptors within the tumor microenvironment that interact with stress-related pathways, as well as investigate potential tumor-type specificity. In-depth exploration of these pathways may provide novel strategies to bolster innate antitumor immunity and optimize therapeutic efficacy.

The effects of exercise on cancer are largely mediated through neural regulation, influencing immune responses and tumor progression via the neuro–endocrine–immune network. Both clinical and preclinical studies have demonstrated that behavioral interventions such as exercise can modulate the immune system and enhance therapeutic efficacy during chemotherapy [322, 323]. In patients, exercise is associated not only with mitigation of cancer- and treatment-related side effects but also with improvements in mental and physical well-being and overall self-reported quality of life [324–326]. Furthermore, behavioral interventions—including regular physical activity, stress management, and sleep optimization—are thought to enhance treatment tolerance, improve psychological status, and potentially influence tumor progression indirectly through immune modulation. Several murine studies have explored the potential synergistic effects of combining exercise with ICIs in cancer therapy [327, 328]. In patient-derived xenograft models of non-small cell lung cancer, anti–PD-1 therapy combined with exercise increased tumor necrosis and reduced apoptosis, suggesting that exercise may potentiate anti–PD-1 efficacy [329]. Another study indicated that 30 min of daily aerobic exercise (treadmill running) enhanced pancreatic tumor sensitivity to anti–PD-1 therapy. This effect was mediated by IL-15Rα$^+$ $CD8^+$ T cell–driven antitumor immune responses, ultimately slowing tumor growth [328]. Additionally, in breast tumor models undergoing anti–PD-1 treatment, voluntary wheel running increased tumor-infiltrating $CD8^+$ T cell numbers, whereas sedentary controls showed no such increase [327, 330]. These preliminary preclinical findings suggest that behavioral regulation, particularly exercise interventions, may enhance antitumor efficacy via immune modulation, providing a theoretical basis for their integration into clinical cancer therapy. Future studies combining multiple behavioral interventions may further optimize treatment outcomes and quality of life for cancer patients.

The circadian rhythm is an intrinsic timing mechanism controlled by the nervous system that regulates various physiological and behavioral activities, including sleep–wake cycles, feeding–fasting patterns, and activity–rest periods. Sleep deprivation or irregular sleep patterns can impair immune function, thereby weakening the body's tumor immune surveillance and clearance capacity. Concurrently, physiological activity and psychological stress during wakefulness may influence immune cell function through neuro–endocrine pathways, further modulating antitumor immune responses [331, 332]. Clinical studies have shown that in patients with advanced lung cancer receiving anti–PD-1 therapy (nivolumab), those treated in the morning exhibited significantly greater antitumor efficacy compared with patients treated in the afternoon [333]. This effect may be related to the rhythmic oscillation of $CD8^+$ T cells within the TME. Therefore, timing immune checkpoint inhibitor administration according to patients' circadian rhythms could potentially enhance therapeutic outcomes [334–336]. Similarly, circadian rhythm–guided radiotherapy and chemotherapy may improve efficacy while reducing adverse effects [337]. Members of the nuclear receptor family, such as RORγ (similar to RORα and RORβ), regulate core circadian genes including BMAL1, CLOCK, and REV-ERBα/β. Preclinical murine studies have demonstrated that RORγ agonists can enhance the antitumor immune responses of CAR-expressing Th17 cells, providing long-term protection against tumors [338]. Currently, a clinical trial is ongoing to evaluate the combination of a RORγ agonist with anti–PD-1 therapy in patients with metastatic NSCLC (NCT03396497). These findings indicate that circadian rhythms not only influence clinical responses to immunotherapy but also provide a rationale for developing novel circadian-based immunotherapeutic strategies. Future research is needed to elucidate how circadian components regulate interactions between cancer cells and the immune system, thereby optimizing the design and application of immunotherapy protocols.

Conclusions

The neuro–immune axis plays a critical role in cancer initiation, progression, and immune evasion, particularly in shaping the tumor microenvironment and regulating T cell and myeloid immune cell functions. Nevertheless, this field faces several challenges and unresolved questions. First, neuro–immune interactions may exhibit high heterogeneity across different tumor types and

tissue contexts, complicating the generalizability of neural intervention strategies. Second, targeting neural signaling pathways may elicit off-target effects, potentially disrupting normal neural function or causing systemic side effects. Additionally, certain neural modulation therapies face limited accessibility due to physiological barriers, such as the blood–brain barrier, which constrains their application in central nervous system tumors. More importantly, many current studies on neural regulation lack precise monitoring of immune responses, limiting both efficacy evaluation and mechanistic understanding. To overcome these challenges, future research in cancer neuroscience should prioritize three directions. First, it is essential to dissect the context-specific nature of neuro–immune interactions across different tumor types and microenvironments, identifying which neural signaling pathways drive immune evasion, tumor invasion, or therapy resistance in specific cancers, thereby guiding targeted interventions. Second, the development of precise, controllable, and localized neural modulation strategies is needed—such as local delivery, reversible or tunable neuromodulation techniques, and patient stratification based on biomarkers—to minimize interference with healthy neural networks and reduce potential side effects. Third, advanced multi-omics and neuroscience technologies should be fully integrated to map the dynamic landscape of neuro–immune networks within tumors. Spatial transcriptomics can resolve the in situ colocalization of nerve fibers and immune cells and reveal local signaling gradients, uncovering the spatial heterogeneity of immunosuppressive or activating niches. Single-cell multi-omics can decode the sensitivity, activation state, and functional differentiation of diverse immune cell populations in response to neural signals, providing a basis for precise prediction of treatment responses. Neural circuit tracing technologies can delineate tumor-associated neural projections and their functional regulatory roles, helping identify key neuro–immune nodes and guiding targeted interventions. By leveraging these multi-layered, high-resolution approaches, researchers can identify novel neurotransmitter–immune receptor axes, define critical nodes of neuro–immune regulation in tumors, and elucidate how neural signaling contributes to immune evasion, inflammation regulation, and therapy resistance in a tumor type-specific manner. Such insights will inform the rational design of combination therapies—including immunotherapy, radiotherapy, chemotherapy, and novel neural-targeted interventions—enabling more precise and personalized treatment strategies.

In summary, integrating neuroscience, immunology, and cancer biology holds promise for establishing the neuro–immune axis as a fifth pillar of cancer therapy, complementing surgery, radiotherapy, chemotherapy, and immunotherapy. For highly treatment-resistant tumors, this approach could offer a new dimension in clinical management. With continuous advances in single-cell omics, spatial transcriptomics, and neural circuit tracing, elucidating the multidimensional neuro–immune–tumor network within the tumor microenvironment will become central to achieving precision oncology.

Abbreviations

5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine
5-HTRs	5-HT receptors
5-HTTP	5-hydroxytryptophan
AADC	Aromatic L-amino acid decarboxylase
AAT	Aspartate aminotransferase
AC	Adenylate cyclase
ACh	Acetylcholine
AChR	Acetylcholine receptors
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
APCs	Antigen-presenting cells
AR	Androgen receptor
AREs	Androgen response elements
BAC	Benzalkonium chloride
cAMP	cyclic AMP
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
CRS	Cytokine release syndrome
DA	Dopamine
DAG	Diacylglycerol
DAMPs	Danger-associated molecular patterns
DAT	Dopamine transporter
DC	Dendritic cell
DRs	Dopamine receptors
E	Epinephrine
EAATs	Excitatory amino acid transporters
EGCs	Enteric glial cells
EMT	Epithelial–mesenchymal transition
ENS	Enteric nervous system
FAO	Fatty acid oxidation
GABA	Gamma-aminobutyric acid
GBM	Glioblastoma
GDH	Glutamate dehydrogenase
GLS	Glutaminase
Glu	Glutamate
GPCR	G-protein-coupled receptor
GR	Glucocorticoid receptor
GSH	Glutathione
HCC	Hepatocellular carcinoma
HPA	Hypothalamic-pituitary-adrenal
HPG	Hypothalamic-pituitary-gonadal
HPT	Hypothalamic-pituitary-thyroid
HSCs	Hepatic stellate cells
ICANS	Immune effector cell-associated neurotoxicity syndrome
IDO	Indoleamine 2,3-dioxygenase
iGluRs	Ionotropic glutamate receptors
IP3	Inositol trisphosphate
ISO	Isoproterenol
KAR	Kainate receptor
mAChRs	Muscarinic ACh receptors
MAO	Monoamine oxidase
MDSCs	Myeloid-derived suppressor cells
MERTK	Mer tyrosine kinase
mGluRs	Metabotropic glutamate receptors
MLT	Melatonin
MSCs	Mesenchymal stem cells
nAChRs	Nicotinic ACh receptors
NE	Norepinephrine
NET	Neutrophil extracellular trap
NGF	Nerve growth factor

NK	Natural killer
NK1R	Neurokinin-1 receptor
NMDAR	N-methyl-D-aspartate receptor
NO	Nitric oxide
NSCs	Neural stem cells
OVA	Ovalbumin
Ovs	Oncolytic viruses
PDTC	Pyrrolidine dithiocarbamate
PKC	Protein kinase C
PLC	Phospholipase C
PNS	Peripheral nervous system
PVN	Paraventricular nucleus
RAMP1	Receptor activity-modifying protein 1
RFA	Radiofrequency ablation
RVLM	Rostral ventrolateral medulla
SCs	Schwann cells
SERT	Serotonin transporter
SSRIs	Serotonin reuptake inhibitors
ST	Standard temperature
TAMs	Tumor-associated macrophages
TANs	Tumor-associated neutrophils
TCA	Tricarboxylic acid
TCR	T cell receptor
TFF2	Trefoil factor 2
TFP	Trifluoperazine
TGM2	Transglutaminase 2
TILs	Tumor-infiltrating lymphocytes
TLRs	Toll-like receptors
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor-alpha
Tpe	T cell phenotype
TPH	Tryptophan hydroxylase
Tsc22d3	TSC22 domain family protein 3
TT	Thermoneutral temperature
VGCCs	Voltage-gated calcium channels
VTA	Ventral tegmental area
α-KG	α-ketoglutarate
α-MSH	α-melanocyte-stimulating hormone
β-ARs	β-adrenergic receptors

Author contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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