Molecular Cancer

REVIEW

Open Access

Neuroscience of cancer: unraveling the complex interplay between the nervous system, the tumor and the tumor immune microenvironment

Qibo Huang[1,2,3,4†], Bai Hu[5†], Ping Zhang[6†], Ye Yuan[7], Shiwei Yue[1,2,3,4], Xiaoping Chen[1,2,3,4*], Junnan Liang[1,2,3,4*], Zhouping Tang[6*] and Bixiang Zhang[1,2,3,4*]

Abstract

The study of the multifaceted interactions between neuroscience and cancer is an emerging field with significant implications for understanding tumor biology and the innovation in therapeutic approaches. Increasing evidence suggests that neurological functions are connected with tumorigenesis. In particular, the peripheral and central nervous systems, synapse, neurotransmitters, and neurotrophins affect tumor progression and metastasis through various regulatory approaches and the tumor immune microenvironment. In this review, we summarized the neurological functions that affect tumorigenesis and metastasis, which are controlled by the central and peripheral nervous systems. We also explored the roles of neurotransmitters and neurotrophins in cancer progression. Moreover, we examined the interplay between the nervous system and the tumor immune microenvironment. We have also identified drugs that target the nervous system for cancer treatment. In this review we present the work supporting that therapeutic agent targeting the nervous system could have significant potential to improve cancer therapy.

Keywords Neuroscience, Nervous system, Neurotransmitters, Tumorigenesis, Tumor immune microenvironment, Neuromodulatory drugs

†Qibo Huang, Bai Hu and Ping Zhang contributed equally to this work.

*Correspondence:
Xiaoping Chen
chenxpchenxp@163.com
Junnan Liang
liangjunnan@tjh.tjmu.edu.cn
Zhouping Tang
ddjtzp@163.com
Bixiang Zhang
bixiangzhang@hust.edu.cn
[1] Hepatic Surgery Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
[2] Hubei Key Laboratory of Hepato-Pancreato-Biliary Diseases, Wuhan, Hubei, China
[3] Clinical Medicine Research Center for Hepatic Surgery of Hubei Province, Wuhan, Hubei, China
[4] Key Laboratory of Organ Transplantation, Ministry of Education, Chinese Academy of Medical Sciences, NHC Key Laboratory of Organ Transplantation, Wuhan, China
[5] Department of Gynecology and Obstetrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
[6] Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
[7] Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China

Introduction

The nervous system is present throughout the body and keeps the organism stable and functioning by transmitting chemical and electrical signals controlled by the central nervous system (CNS) [1, 2], the appetite, and the energetic metabolism. Since the twentieth century, scientists have begun to focus on the crosstalk between the tumor microenvironment and the nervous system [3–5]. Increasing evidence has shown that neurological dysregulation is highly correlated with tumorigenesis and progression [6–9]. The brain performs different neurological functions in each specific area and is directly or indirectly related to complex body behaviors or diseases [10–12]. In the hypothalamus, chronic stress affects tumor development and the immune system, which is mediated by the paraventricular nucleus (PVN) through the hypothalamic–pituitary–adrenal (HPA) axis [13] and the sympathetic-adrenal system (SAS) [14]. The disruption of the circadian rhythm affects the suprachiasmatic nucleus (SCN), which changes the tumor microenvironment of tumor cells and immune cells [15–18]. Beyond the hypothalamus, the prefrontal cortex (PFC), amygdala, ventral tegmental area (VTA), and the autonomic nervous system (ANS), contribute to the modulation of cancer onset and progression [11, 19–21]. Neurotransmitters affect cancer progression by activating the corresponding receptor pathways in tumor cells or immune cells [22–24]. The interaction between the nervous system and the tumor immune microenvironment is of significant importance [25]. Therefore, the elaborate balance of the nervous system, tumorigenesis, and tumor immune microenvironment is becoming increasingly apparent, highlighting the potential to harness neurobiological mechanisms in cancer therapy [6, 26–29].

In this review, we explored the complex interactions between the nervous system, cancer progression, and the tumor immune microenvironment. Moreover, we explored the impact of stress on tumor growth via the HPA axis and SAS, disruption of circadian rhythms on immune cell dynamics, and the influence of neurotransmitters such as dopamine, glutamate, serotonin, and gamma-aminobutyric acid (GABA) on cancer cell behavior. The impact of the nervous system on the tumor immune microenvironment was also examined. Furthermore, we considered the therapeutic potential of neuromodulatory drugs and emerging strategies that leverage the influence of the nervous system on cancer for novel treatment approaches. This review highlights the burgeoning field of cancer neuroscience and its potential to tumor immune microenvironment and cancer therapy.

Nervous system regulation on tumorigenesis and cancer progression

Neurological functions in central nervous system impact on tumorigenesis and cancer progression

Stress

PVN is a midline thalamic structure adjacent to the third ventricle that controls stress, arousal, emotional memory, motivation, metabolism, and immunity [30, 31]. Stress experiences are divided into physical stressors (toxins and pathogens) and psychological stressors (schizophrenia, depression, harmful, abusive, and environmental factors of the community environment) [32]. These stressful experiences are related to the regulation of the immune system, which affects tumor development and prognosis [33–35]. However, the way in which the nervous system, tumor, and immune systems communicate is not well understood. The effect of stress on tumors and the immune system is mediated primarily by the HPA axis [13] and the SAS [14], the two main functional axes through which the hypothalamus functions [36, 37]. Glucocorticoid synthesis is controlled by the HPA axis, which produces cortisol as the main glucocorticoid in humans [38–40]. Glucocorticoids have been confirmed to promote breast cancer metastasis by activating the glucocorticoid receptor in tumor cells and play an immunosuppressive role in orthotopic and patient-derived xenograft models [41]. Furthermore, glucocorticoids dictate the dynamics of circulating tumor cell generation in patients with breast cancer and mouse models [42].

In addition to the HPA axis, catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) are produced and secreted in the medulla of the adrenal gland and are regulated by stress through SAS [43–45]. The role of SAS in cancer was first studied in an orthotopic ovarian cancer xenograft mouse model in which conditions such as physical restraint or periodic immobilization were applied, while the HPA axis remained active, blocking the β-adrenergic pathway ceased tumor progression [46]. Additionally, the discharge of catecholamines can trigger the HPA axis, which is regulated by the PVN, via noradrenergic neurons located in the nucleus of the solitary tract [47]. The observed reduction in tumor progression in a murine stress model following total adrenalectomy or surgical laparotomy indicates that neuroendocrine axes are among the multitude of influential factors, and their activity can be modulated by diverse brain regions [48] (Fig. 1, Table 1).

Circadian rhythms and wakefulness

The World Health Organization's International Agency for Research on Cancer designated circadian rhythm disruption as a probable carcinogen to humans in 2007 [49]. Circadian rhythms include sleep–wake cycles,

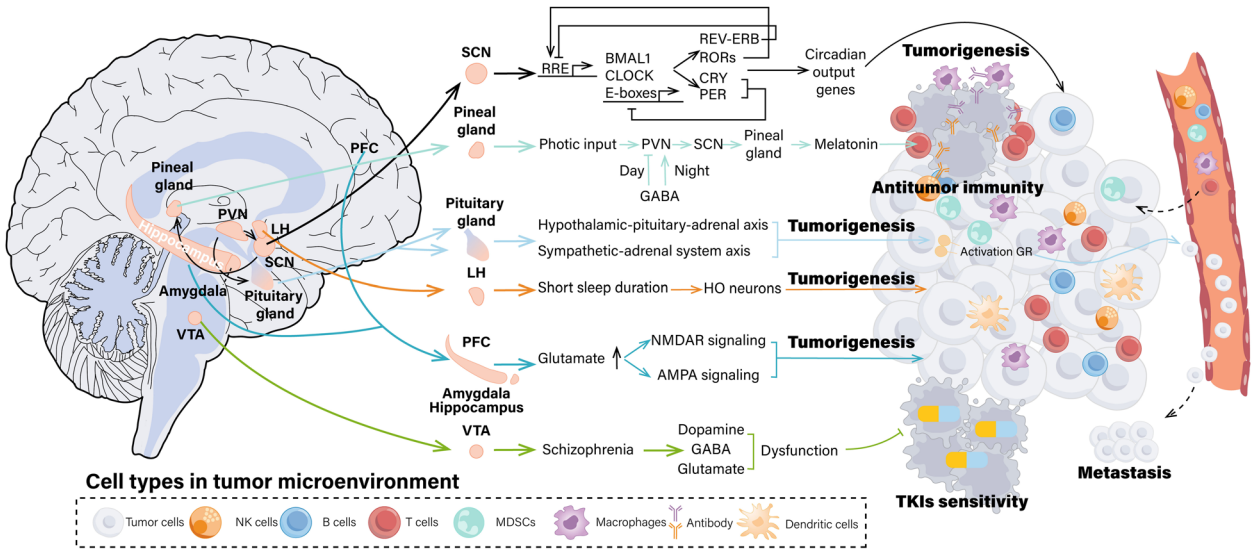

Fig. 1 Neurological functions in central nervous system involved in tumorigenesis and progression. Neurological function, including stress, circadian rhythms, wakefulness, cognitive processes and emotional responses regulated by the central nervous system impacts on cancers. Stress affects the paraventricular nucleus (PVN), which influence on the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic-adrenal system (SAS) is crucial for stress-related immune modulation and tumor progression. The suprachiasmatic nucleus (SCN), which governs circadian rhythms contributes to tumorigenesis and tumor immune microenvironment. Wakefulness regulated by the lateral hypothalamus (LH) impacts on cancer progression. Cognitive and emotional regulation by the prefrontal cortex (PFC), amygdala, and hippocampus are affected in cancer patients and cancer therapies

eating-fasting patterns, activity-rest cycles, and day-night cycles, which ensure the coordination of organ functions and physiological processes throughout the body to achieve and maintain homeostasis [50–52].

In mammals, the SCN of the anterior hypothalamus serves as the principal circadian pacemaker [53, 54]. Pituitary tumors and vascular diseases in humans disrupt daily rhythms, and SCN-ablated animals can restore rest-activity rhythms by grafting neonatal SCN tissue [53, 55, 56]. Circadian rhythm mechanisms encompass various biological processes such as the synthesis and breakdown of molecules, cell cycle, immune cell activities, programmed cell death, and repair mechanisms for DNA damage [57, 58]. Growing evidence suggests a relationship between chronic disturbances in circadian rhythms and tumorigenesis [59–62]. Activity-rest cycles have been identified as a significant factor in patients with metastatic colorectal cancer (CRC) [63]. In breast cancer-prone $p53^{R270H/+}$ WAPCre conditional mutant mice, chronic circadian rhythm disturbances promote the development of breast cancer [64]. In addition, night shift work and the disruption of circadian clock genes have been associated with the progression of breast, prostate, and lung cancer [65–67]. The photic input of the retina to the SCN is regulated by adenosine 3′,5′-monophosphate (cAMP) signaling, neuropeptides vasoactive intestinal polypeptide, and neurotransmitter GABA signaling [68–70]. Positive regulators of circadian transcription proteins are circadian locomotor output cycles kaput (CLOCK), brain, and muscle aryl hydrocarbon receptor nuclear translocator 1 (BMAL1), which bind to cryptochrome (Cry) and period (Per) genes with their E-boxes through two helix-loop-helix domains [71–73]. Although CRY and PER interact with casein kinase Iε as a heterodimer, their function has a negative effect on CLOCK/BMAL1-driven transcription [74–77]. Furthermore, circadian genes are transcriptionally upregulated or downregulated by Rev-erbα (Nr1d1) and Rev-erbβ (Nr1d2) or retinoid-related orphan receptors [78–80].

The circadian genes associate with tumorigenesis. In CRC patients, the mutation of the pivotal circadian clock gene Per2 has been implicated in the augmentation of intestinal and colonic tumorigenesis in the $Apc^{Min/+}$ model, mediated through the upregulation of the β-catenin signaling cascade [81]. In addition, loss of Per2 and BMAL1 accelerates $Kras^{G12D}$ mutation-mediated lung cancer progression [66]. Furthermore, researchers have reported the tumor suppressive role of Per2 in different cancers [82–85]. Peng et al. showed that sleep deficiency continuously promotes the production of palmitoyl-coenzyme A catalyzed by long-chain fatty acyl-CoA synthetase 1, which facilitates CLOCK-Cys194 S-palmitoylation, fatty acid oxidation (FAO)-sensed circadian disruption, and enhanced tumorigenesis [86].

Table 1 Neurological function and related brain region in tumorigenesis

Neurological Function	Pro/Anti-Cancer	Related Brain Region	Main Effects and Affected Pathways	References
Stress	Pro-cancer	Paraventricular nucleus (PVN)	Activation of the HPA axis leads to increased glucocorticoids, which promotes tumor progression and metastasis through glucocorticoid receptor activation on tumor cells	[13] [33–48],
Circadian Rhythms	Anti-cancer	Suprachiasmatic nucleus (SCN)	Disruption of circadian rhythms impacts the molecular synthesis, cell cycle, immune cell activities, programmed cell death, and DNA damage repair mechanisms. Mutations in circadian genes like Per2 can upregulate β-catenin signaling pathways, promoting intestinal and colonic tumorigenesis. Loss of circadian clock genes is associated with the progression of various cancers	[15–18] [49–90],
Wakefulness	Pro-cancer	Lateral hypothalamus (LH)	The HO neurons influence the HPA axis and sympathetic nervous system, leading to increased corticosterone secretion which has immunosuppressive effects and promotes cancer cell behavior. The activation of HO neurons also modulates the body's response through changes in the HPA axis and sympathetic nervous system activity	[91–106]
Cognitive and Emotional Responses	Pro-cancer	Prefrontal cortex (PFC), Amygdala, Hippocampus, Ventral tegmental area (VTA)	Stress-induced alterations in brain regions involved in cognition and emotion can lead to structural changes, affecting neuronal function. Glutamate, acting on NMDA and AMPA receptors, modulates neuronal excitability and has been implicated in the growth of gliomas, PDAC, and breast to brain metastasis. Antipsychotic drugs are used in cancer treatment which has a antitumor effect	[107–133, 139, 140, 142, 143]

However, BMAL1 deletion suppressed tumorigenesis in a RAS mutation-triggered cutaneous squamous tumor model [87].

GABA influences SCN activity by inhibiting PVN autonomic neurons during the day and enabling their activation at night. This mechanism regulates the cyclical secretion of melatonin by the pineal gland, which controls the sleep–wake pattern [88]. Melatonin in the bloodstream enhances immune responses by binding to melatonin receptors present in immune cells [89]. Furthermore, melatonin has been shown to increase effector and regulatory T cells, which are associated with antitumor immunity [90].

The lateral hypothalamus (LH) is a vital region to regulate wakefulness, which is related to appetitive and consummatory behaviors through lateral hypothalamic GABAergic neurons (LH^{GABA}) [91–93]. Hypocretin/orexin (HO) neurons, which secrete the neuropeptide hypocretin (HCRT; Orexin), play an essential role in inflammatory disorders and wakefulness [94–97]. These two significant efferent outputs from the HO system cause changes in body functions and cancers on both the HPA axis and the sympathetic nervous system [97]. Activation of HO neurons caused by hyperarousal promotes corticosterone secretion, which has multiple effects on the immune system and cancers [98, 99]. Furthermore,

the sympathetic nervous system is partly included in LH, and HO neurons can activate the sympathetic nervous system to modulate multiple body responses [100]. Yi et al. reported that HO neurons are essential for hepatic gluconeogenesis through the sympathetic nervous system [101], and Borniger et al. used a dual HO-receptor antagonist to identify metabolic abnormalities caused by HO signaling activation, which uncovered the metabolic and sleep abnormalities that infected central neuromodulators, contributing to breast cancer progression [102]. Sleeping behavior is a key factor in maintaining HO release, which modulated hematopoiesis [103–106]. Collectively, the mechanism by which circadian rhythms and wakefulness influence cancer development requires further exploration (Fig. 1, Table 1).

Cognitive processes and emotional responses

The PFC, amygdala, and hippocampus regulate cognitive function, emotions, and behaviors [107, 108]. These brain regions can be impaired in individuals experiencing cognitive decline or in those diagnosed with psychiatric disorders [109, 110]. Reports indicate that cognitive deterioration is observed in individuals with breast cancer or CRC [111], and a significant debilitating consequence of systemic cancer treatment is the impairment of cognitive function [112, 113]. Patients exhibited greater cognitive deficits compared to healthy individuals, and the etiology of cognitive impairment is hypothesized to result from direct tumor invasion, paraneoplastic syndrome, and distant metastasis [114]. In another study, patients with localized breast cancer had a higher cognitive impairment before any cancer treatment, which was mostly related to fatigue [115].

Stress has a significant impact on the reshaping of the brain structure, especially the PFC, amygdala, and hippocampus [116–118]. Therefore, the brain regions can change owing to long-term exposure to stress or long-term use of glucocorticoids, which can lead to modifications in neuronal structures or dendritic reorganization [119–121]. Moreover, the neurotransmitter glutamate acts in multiple areas of the brain by binding to specific glutamate receptors, such as N-methyl-d-aspartate (NMDA) receptors [122], α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptors (AMPA), and Kainate receptors, regulating neuronal excitability [123]. These glutamate receptors are abundant in PFC, amygdala and hippocampus [124]. Glutamate has been reported to act as a growth factor in gliomas [125], pancreatic ductal adenocarcinomas, and breast-to-brain metastasis (B2BM) [126–128]. Dizocilpine, an antagonist of the NMDA receptor, and GYKI52466, an antagonist of the AMPA receptor, both demonstrate antiproliferative effects on cells derived from colon adenocarcinoma, astrocytoma, and carcinomas of the breast and lung [129]. In B2BM cells, activation by glutamate ligands of N-methyl-D-aspartate receptors (NMDAR) has been identified as a key signaling pathway for breast cancer metastatic colonization of the brain, implicating invasive tumor growth [130].

In patients with schizophrenia, the functional connectivity of the VTA can be altered, which could be related to cognitive dysfunction, emotional blunting, and abnormalities in reward processing experienced by patients [131, 132]. Some studies have indicated that reduced functional connectivity between the VTA and brain regions, such as the prefrontal cortex, ventral pallidum, and nucleus accumbens, may be associated with the severity of schizophrenia symptoms. Neurons within the VTA that emit dopamine are central to the modulation of behaviors linked to reward seeking, decision processes, working memory, the prominence of incentives, the significance of stimuli, and avoidance reactions [131, 132]. Dopamine-producing neurons in the VTA, which express the enzyme tyrosine hydroxylase (TH) and release dopamine, are regulated by various brain regions as well as by local GABA and glutamate neurons within the VTA itself [133]. GABA, glutamate, and dopamine are involved in normal brain information processing; however, patients with schizophrenia who suffer from behavioral and cognitive dysfunction have a neurotransmitter problem [134]. Therefore, patients with schizophrenia have a high mortality rate for cervical cancer, breast cancer, and CRC, which is partly owing to inappropriate cancer screening and difficulties in coping with treatment [135, 136]. Antipsychotic drugs are the main treatment for schizophrenia, including clozapine and chlorpromazine, which act as dopamine D2 receptor antagonists [137, 138]. Recent studies have shown that chlorpromazine inhibits cancer progression and promotes drug sensitivity [139]. In non-small cell lung cancer (NSCLC), resistance to tyrosine kinase inhibitors (TKIs) is primarily driven by the T790M mutation in the epidermal growth factor receptor (EGFR). Combination treatment with chlorpromazine and TKIs can restore sensitivity to gefitinib in TKI-resistant cells [140]. Furthermore, a chlorpromazine derivative (JX57) was confirmed to inhibit endometrial cancer progression through the GRP75-AMPK axis [141]. Similarly, chlorpromazine induces apoptosis and G2/M phase arrest in oral and colorectal cancer [142, 143] (Fig. 1, Table 1).

Peripheral nervous system impact on tumorigenesis and cancer progression

Neurogenesis in tumor microenvironment regulation

The peripheral nervous system extends from the central nervous system and encompasses the sympathetic

nervous system (SNS), parasympathetic nervous system (PNS), and enteric nervous system. It acts as a homeostatic regulator, managing bodily functions such as blood pressure, heart rate, gastrointestinal motility [144, 145] and the immune system [146]. Functionally, the "fight or flight" response is regulated by the SNS by promoting the cardiovascular organ [147]. In contrast, the "rest and digest" response is regulated by PNS by decreasing heart rate and increasing digest function [148]. Noradrenaline is the neurotransmitter of the SNS, recognized by α-adrenergic and β-adrenergic receptors. Acetylcholine (ACh) is a neurotransmitter of the PNS and is recognized by the nicotinic and muscarinic ACh receptor [12]. Consequently, the critical role of ANS in peripheral tumors involves modulating the microenvironment, affecting tumor growth and metastasis, and potentially influencing the patient's response to the treatment, warranting increased attention [149–152]. As embryonic development requires the formation of the nervous system through neurogenesis, the production of blood cells through hematopoiesis, the establishment of blood vessels through angiogenesis, primary tumor tumorigenesis, and metastasis also depend on the establishment of interconnected networks of the nervous, immune, and vascular systems [153]. The expansion of nerve fibers from existing nerves is stimulated by neurotrophic factors that are produced and discharged into the tumor microenvironment. This process leads to the formation of nerve networks associated with the tumor, which in turn produce neural signals that play a role in controlling the development and spread of cancer [8, 154, 155]. Neural progenitor cells, characterized by the expression of doublecortin (DCX^+), have been localized to the subventricular zone (SVZ) and are known to traverse the blood–brain barrier, infiltrate prostate tumors, and modulate tumorigenesis [156]. Moreover, overexpression of semaphorin 4F increases nerve density through tumor axonogenesis and neurogenesis, which could contribute to the crosstalk between nerve fibers and cancer cells [157, 158]. Granulocyte colony-stimulating factor has neurotrophic properties that enhance nerve spread in prostate tumor [154]. In gastrointestinal malignancies, enteric neural progenitors exhibit superior regenerative capacities compared to CNS progenitors [159]. Glioblastoma cells promote tumor neurogenesis by activating PI3K/AKT and CDC42. Furthermore, glioblastoma stem cells invade the SVZ via the CXCL12/CXCR4 axis [160]. Collectively, these studies underscore the crucial role of neurogenesis in TME (Fig. 2, Table 2).

Sympathetic nervous system

Chronic stress promotes cancer development [35, 161]. Catecholamines, the main neurotransmitters that play a vital role in the stress response, are strongly correlated with tumorigenesis and development [162, 163]. The fibers of the SNS and receptors of SNS neurotransmitters are widely distributed in the pancreas, making pancreatic cancer sensitive to neural signaling [164–166]. Furthermore, SNS fibers also innervate in the bone marrow, and chronic stress promotes acute lymphoblastic leukemia progression via β-adrenergic signaling pathway mediated by other host cell type [167]. β-blocker propranolol also had an antiproliferation effect on myeloma cells, indicating that stress hormones could be an essential part of multiple myeloma [168].

In DEN-induced hepatocarcinogenesis, adrenaline promoted hepatocellular carcinoma (HCC) proliferation, which could be reversed by β2 antagonists (ICI-188,551 and butoxamine). In this mechanism, adrenaline inhibited autophagy by disrupting Beclin1/VPS34/Atg14 complex, leading to HIF1α stabilization. Inhibition of β2-adrenergic signaling also improved sorafenib sensitivity in HCC [169].

Magnon et al. observed autonomic nerve fibers in the prostate gland in mouse models, while sympathectomy or genetic deletion of stromal β2/3 adrenergic receptors could prevent tumor development [155]. In addition, β-adrenergic receptor signaling activated by noradrenaline is significant in the angiogenic switch, which promotes the development of prostate cancer. Although deletion of Adrb2, the gene encoding β2-adrenergic receptor could inhibit prostate cancer progression by blocking endothelial oxidative phosphorylation [170]. Furthermore, SNS and PNS densities were associated with a poor survival rate [155].

Catecholamine depletion by 6-hydroxydopamine attenuates tumor neovascularization and inhibits tumor progression. Notably, catecholamines improved tumor neovascularization by promoting VEGF expression secreted by polarized M2 macrophages. Meanwhile, blocking catecholamines creates an immunosuppressive microenvironment in which myeloid-derived suppressor cell (MDSCs) recruitment is reduced and dendritic cells (DCs) are activated [28, 162]. Chemically induced breast cancer progression can be regulated by sympathetic and parasympathetic nerves, in which sympathetic nerves have a promoting role, while parasympathetic nerves have an inhibiting role [171] (Fig. 2, Table 2).

Parasympathetic nervous system

In cancer progression, the PNS serves a complex role. Specifically in pancreatic ductal adenocarcinoma (PDAC), the formation of PNS nerves is linked to tumor initiation and is a marker of unfavorable outcomes [172]. Additionally, the muscarinic acetylcholine receptor 3 [173–176], a muscarinic receptor in the PNS, is

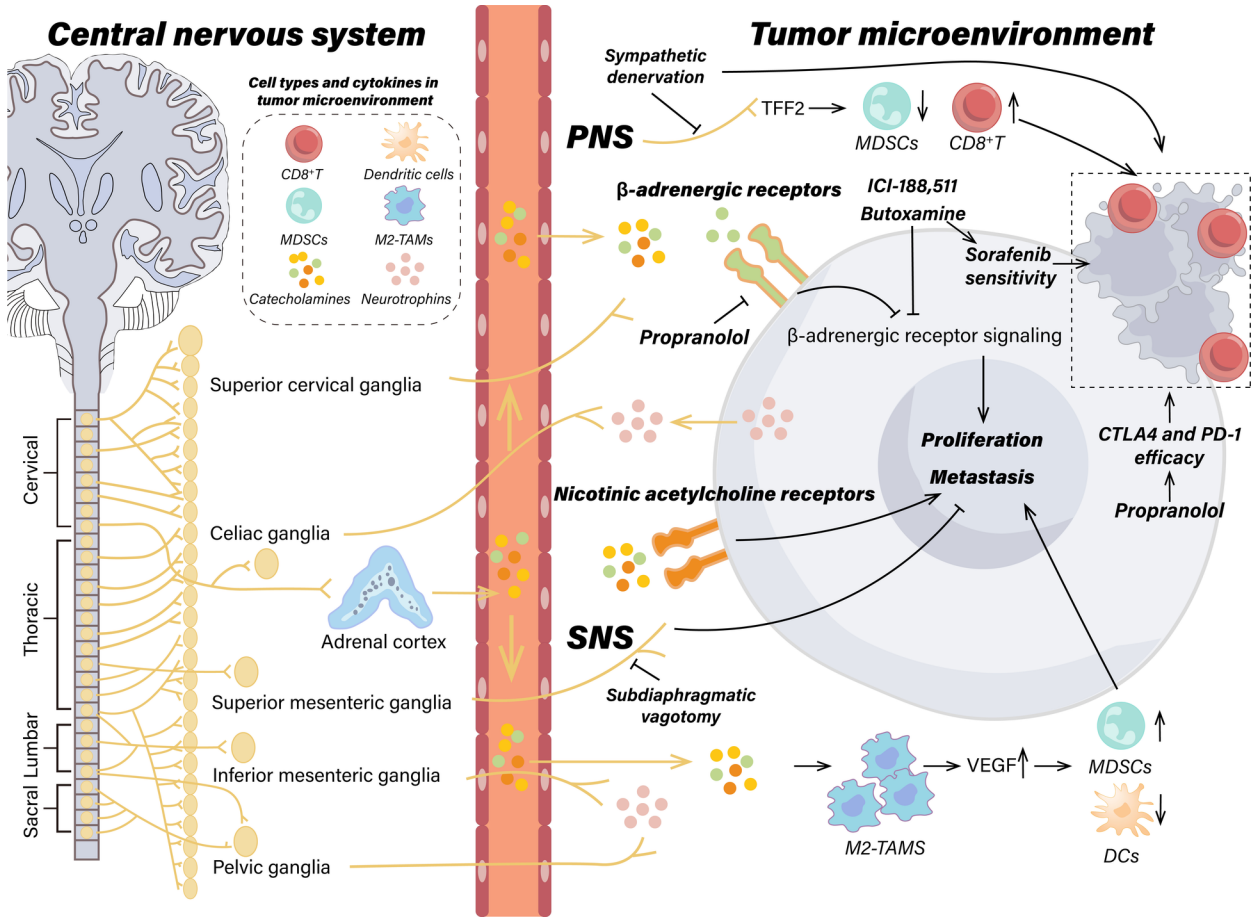

Fig. 2 The peripheral nervous system involved in tumorigenesis and progression. The peripheral nervous system significantly contributes to tumor microenvironment regulation through the sympathetic nervous system (SNS), parasympathetic nervous system (PNS), and enteric nervous system. During development, the superior cervical ganglia (SCG), the prevertebral sympathetic ganglia, the celiac ganglia (CG), the superior mesenteric ganglia (SMG), the inferior mesenteric ganglia (IMG), and the pelvic ganglia (PG) extend axonal projections to supply and interact with various peripheral organs and tissues. The neurogenesis within the SNS and PNS, stimulated by neurotrophic factors in the tumor microenvironment, leads to the formation of nerve networks that influence cancer development and spread. The vagal nerve is shown to modulate memory T cells and suppress MDSC expansion through the secretion of the anti-inflammatory peptide TFF2. β-blockers, such as propranolol, exhibit antiproliferative effects on myeloma cells and enhance the efficacy of immunotherapies targeting CTLA4 and PD-1. Adrenaline in hepatocellular carcinoma (HCC) proliferation is important, along with the reversal of this effect by β2 antagonists, which also improve sorafenib sensitivity in HCC. Catecholamine depletion is depicted as a means to reduce tumor neovascularization and progression, with an emphasis on its effect on VEGF expression by M2 macrophages and the subsequent immunosuppressive microenvironment. Lastly, sympathetic and parasympathetic nerves denervation suppress cancer progression

upregulated in HCC tumors and is correlated with a poor survival rate in PDAC [177, 178].

In contrast, subdiaphragmatic vagotomy in a murine pancreatic cancer model increased colon carcinogenesis and tumor progression [179, 180]. Nicotine and acetylcholine acts as ligands for nicotinic acetylcholine receptors (nAChRs) including, α5, α7, β2, β4, which are expressed not only in the nervous system but also in NSCLC. Among these, α7 nAChR and heteromeric α5, β2, β4 nAChRs were found to promote tumor progression by enhancing invasion and regulating tumor proliferation [181].

In summary, increasing evidence suggests that the brain exerts specific and targeted control over the immune system, a function facilitated by ANS. From a physiological perspective, the SNS and PNS, along with their local and hormonal mechanisms, serve as a means for the body to maintain balance and stability. Denervation or adrenergic receptor blockers may be therapeutic solutions for cancer development [28] (Fig. 2, Table 2).

Table 2 Peripheral nervous system and tumorigenesis

Peripheral Nervous System	Pro/Anti-Cancer	Cancer Type	Mechanism	References
Sympathetic nervous system (SNS)	Pro-cancer	PDAC	Extensive distribution of SNS fibers and their neurotransmitter receptors in the pancreas, influencing tumor growth and metastasis through neural signaling	[164–166]
		ALL	Chronic stress promotes the progression of ALL via the β-adrenergic signaling pathway mediated by other host cell types	[167]
		HCC	Adrenaline promotes HCC proliferation by disrupting autophagy through the Beclin1/VPS34/Atg14 complex, leading to HIF1α stabilization	[169]
Parasympathetic nervous system (PNS)	Dual role	PDAC	PNS neurogenesis is associated with stimulating tumors and poor prognosis. Vagotomy or genetic deletion of stromal β2/3 adrenergic receptors can prevent tumor development	[172, 179, 180, 324, 325]
		NSCLC	Nicotinic acetylcholine receptors (nAChRs) expressed in NSCLC, where α7 nAChR and heteromeric α5, β2, β4 nAChRs promote tumor progression by enhancing invasion and regulating tumor proliferation	[181]

The role of synapse, neurotransmitters and neurotrophins in cancer

Synapse

Synaptic genes and synapse input are found in brain tumors [128, 182] and the interaction between synapse and cancer cells is a key aspect of the pathophysiology of cancers [183–185]. Neurogliomal synapses were found in tumor microtubes generate AMPA receptor-driven postsynaptic currents which enhanced tumor growth and invasion [125]. NMDAR activation is achieved through the formation of pseudo-tripartite synapses between cancer cells, and glutamatergic neurons induce breast-to-brain metastasis [130]. Moreover, the close-range interactions between immune cells and the synaptic produce different effects on fine tuning of the immune response [186, 187] or participating in synapse elimination and plasticity [188–190].

Collectively, therapies aimed at specific glutamate receptor subtypes, post-synaptic signaling pathways, or the processes essential for synapse formation could potentially serve as treatment targets to decelerate brain tumor growth [191]. This raises the question of whether synapse formation exists in other tumor types and the related mechanisms need to be further explored.

Dopamine

Dopamine (DA), a crucial monoamine neurotransmitter in the CNS, is also known as a catecholamine [192]. It is produced in the basal ganglia, digestive tract, spleen, and pancreas [193, 194]. DA plays a role in cognition [195], behavior [196, 197], affective state transition [198], addiction [199], and reward system [200]. Elevated circulating dopamine concentrations are observed in the plasma of individuals with lung cancer, and it has been demonstrated that dopamine suppresses the proliferation and cytotoxic capabilities of T cells [201].

Dopamine D1 receptors (DRD1) play an inhibitory role in osteosarcoma OS732 cells through the ERK1/2 and PI3K/AKT signaling pathways [202]. The DRD1 inhibitor SKF83566 inhibits glioblastoma (GBM) proliferation and invasion through the DRD1-c-Myc and UHRF1 axes [203]. Additionally, immune cells including lymphoid and myeloid lineages express DA receptors [194, 204].

Dopamine receptor D2 (DRD2) suppresses certain cancer-related characteristics and is found to be overexpressed in various types of cancer including gastric, cervical, lung, and breast cancer [205–209]. In breast cancer, DRD2 enhanced M1 macrophages, restricted NF-κB signaling, and triggered pyroptosis [210]. Given the significant role of DRD2, research has been conducted to explore its potential as a therapeutic target [211, 212]. The agonist of the DRD2, bromocriptine, suppressed the expression of the c-Myc oncogene and enhanced the levels of the tumor suppressor proteins p53, p21, and p27. The concurrent use of bromocriptine with docetaxel heightened the cytotoxic effect on prostate cancer cells and slowed the progression of bone metastasis in prostate cancer [213]. In drug-resistant and metastatic breast cancer, the DRD2 antagonist sulpiride enhances the dexamethasone response by decreasing MMP-2 expression [214]. As a DRD2 antagonist and a butylbenzene

antipsychotic, haloperidol initiates ferroptosis and boosts the effectiveness of temozolomide. Mechanistically, haloperidol antagonizes DRD2 activity, which induces autophagy and ferroptosis and enhances chemoradiotherapy in GBM [215]. A separate study found that DRD2 antagonists such as thioridazine, pimozide, haloperidol, and remoxipride reduced the formation of spheroids in U87 GBM cells, whereas DRD2 agonists like PHNO, sumanirole, and ropinirole promoted spheroid formation in these cells [216]. NMDAR in the spinal cord is essential for the experience of chronic pain and is influenced by the dopamine receptors DRD1 and DRD2. Additionally, blocking DRD1 and DRD2 with antagonists has been found to decrease levels of p-NR1, p-NR2B, Gq protein, p-Src, spinal CGRP, and c-Fos, thereby providing relief from bone cancer-induced pain [217]. In addition, DRD5 is expressed in human pituitary adenomas, glioblastomas, colon cancer, and gastric cancer, while SKF83959, an agonist of DRD5, suppresses tumor proliferation by inhibiting mTOR activity and inducing autophagy [23] (Fig. 3, Table 3).

Glutamate

In the CNS, glutamate is the main excitatory neurotransmitter that mediates excitatory signals to maintain biological functions [218–220]. Glutamate has been demonstrated to be involved not just in learning and memory processes, but also in the bioenergetic, biosynthetic, and metabolic capabilities that contribute to oncogenesis [221–223]. It has been reported that excitotoxic concentrations of glutamate were released by glioma cells [224].

Glutamate receptors, including inotropic receptors (iGluRs) and metabotropic receptors (mGluRs), are involved in malignant diseases of breast cancer, prostate cancer, lung cancer, CRC, melanoma, osteosarcoma, multiple myeloma, glioma, medulloblastoma, and

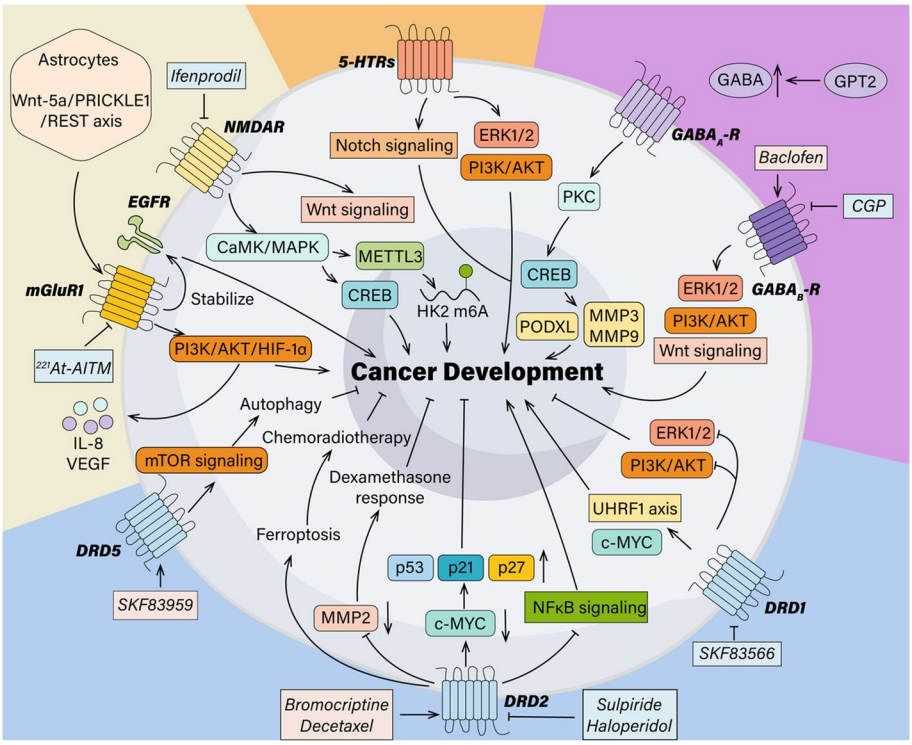

Fig. 3 The role of neurotransmitters and its receptors in cancer progression. Neurotransmitters exert significant influence cancer progression through specific signaling pathways. Dopamine modulates cancer cell behavior via the D1 and D2 receptor pathways, DRD1 inhibits osteosarcoma cell growth through ERK1/2 and PI3K/AKT pathways, while DRD2 inhibits breast cancer by NF-κB signaling. DRD1 inhibitor SKF83566 inhibits tumor proliferation through DRD1-c-Myc and UHRF1 axes. The agonist of the DRD2, bromocriptine, enhanced the levels of the tumor suppressor proteins p53, p21, and p27. The concurrent use of bromocriptine with docetaxel heightened the cytotoxic effect on tumor cells. SKF83959 inhibits DRD5 which induce autophagy via mTOR signaling. 221At-labelled mGluR1 inhibitor, 221At-AITM, induces senescence of tumor cells and exerts antitumor effects in multiple tumors. mGluR1 also triggered by astrocytes through the Wnt-5a/prickle planar cell polarity protein 1/RE1 silencing transcription factor axis. The role of the NMDAR, activate MAPK and CaMK which lead to activation of CREB transcription factor and m^6A modification. NMDAR antagonist ifenprodil synergized with sorafenib downregulated genes in WNT signaling. 5-HTRs are shown to promote cancer cell proliferation through Notch signaling, MAPK, and PI3K/Akt pathways. GABA receptors influence tumor growth through Wnt signaling, MAPK, PI3K/Akt pathways and the $GABA_A$-R-PKC-CREB axis which can be influenced by $GABA_B$-R agonist Baclofen or $GABA_B$-R antagonist CGP

Table 3 The role of neurotransmitter and neurotrophins in cancer progression

Neurotransmitter, neurotrophins	Receptors	Pro/Anti-cancer	Cell Type	Mechanism	Inhibitor	Agonist	References
Dopamine (DA)	D1 receptor (DRD1)	Anti-cancer	Osteosarcoma	Suppressed ERK1/2 and PI3K/AKT signaling pathways			[202]
		Pro-cancer	Glioblastoma	Promoted cancer proliferation and stem cell sphere formation though DRD1-c-Myc and UHRF1 axis	SKF83566		[203]
	D2 receptor (DRD2)	Anti-cancer	M1 macrophages	Triggered pyroptosis			[210]
		Anti-cancer	Prostate cancer cells	Inhibited the expression of c-Myc and increased the expression of p53, p21 and p27		Bromocriptine	[213]
		Pro-cancer	Breast cancer cells	Decreased MMP-2 expression	Sulpiride		[214]
		Pro-cancer	Glioblastoma	Induced autophagy and ferroptosis	Haloperidol		[215]
Glutamate	mGluR1	Pro-cancer	Multiple common tumor cells	Induced senescence of tumor cells	^{211}At-AITM		[229]
		Pro-cancer	Prostate cancer cells	Decreased tumor growth in PTEN wild-type-PI3K/AKT mutant			[230]
		Pro-cancer	Lung cancer cells	Stabilized EGFR and induced lung cancer brain metastasis			[231]
	NMDAR	Pro-cancer	Tumor cells	Activated the CREB			[241, 242]
		Pro-cancer	Hepatocellular carcinoma cells	Upregulated gene in WNT signaling and stemness	Ifenprodil		[243]
		Pro-cancer	pancreatic ductal adenocarcinoma	NMDAR activated Ca^{2+} dependent protein kinase CaMKII/ERK-MAPK pathway, upregulated m6A modification and HK2			[247]
		Anti-cancer	T cells	Suppressed MDSCs though the JNK-NMDAR-ARG-1 pathway	MK801		[248]

Table 3 (continued)

Neurotransmitter, neurotrophins	Receptors	Pro/Anti-cancer	Cell Type	Mechanism	Inhibitor	Agonist	References
Serotonin (5-HT)	5-HTR1B,2B	Pro-cancer	Hepatocellular carcinoma cells	Induction of cancer cell proliferation and drug resistance via Notch signaling			[257–260]
	5-HTRs	Pro-cancer	Tumor cells	Activated downstream pathways including the adenylyl cyclase, MAP kinase, and PI3K/Akt pathways promoted cancer cells proliferation and inhibited apoptosis			[262, 263, 265–271]
		Anti-cancer	T cells	Serotonylation of GAPDH Q262 induced $CD8^+$ T cell glycolytic metabolism			[272]
		Anti-cancer	B Cells, NK Cells	Activation of antitumor immunity; modulation of immune cell activity	(+) WAY 100135	8-OH-DPAT	[273] [274],
GABA (γ-aminobutyric acid)	GABRP	Pro-cancer	Pancreatic ductal adenocarcinoma cells	Promoted Ca2 + entry by interacting with KCNN4 which activated nuclear factor κB signaling leading to macrophage infiltration			[279]
	$GABA_AR$	Pro-cancer	Breast cancer cells	$GABA_AR$-PKC-CREB signaling which led to upregulation of PODXL, MMP3 and MMP9			[22]
	$GABA_BR$	Pro-cancer	Chondrosarcoma cells	Inhibited G1/S cell cycle checkpoint and induced apoptotic pathways via inhibition of MAPK and PI3K/AKT/mTOR signaling pathway	CGP	Baclofen	[283, 284, 286]
NGF	TrkA	Pro-cancer	Melanoma cells	Autocrine NGF activates TrkA, decreasing interferon γ signaling and leading to T and NK cell exclusion	Larotrectinib		[295]
		Pro-cancer	Bone metastases prostate cancer	Fbxo22 ubiquitinated KLF4 impacted NGF/TrkA axis by repressing NGF transcription	GW441756		[296, 297]

Table 3 (continued)

Neurotransmitter, neurotrophins	Receptors	Pro/Anti-cancer	Cell Type	Mechanism	Inhibitor	Agonist	References
BDNF	TrkB	Pro-cancer	HCC and ovarian cancer cells	BDNF/TrkB pathway enhances cancer proliferation, invasion, and migration			[293, 299, 300]
		Pro-cancer	CAFs	BDNF from CAFs enhances TrkB-Nrf2 signaling in GC cells, suppressing anlotinib-induced apoptosis and ROS			[301]

few leukemias [225–228]. iGluRs are categorized into NMDAR, AMPAR, and kainate receptors, while mGluRs are segregated into three subfamilies: groups I, II, and III [126, 222]. In 32 different tumor types, mGluR1 was abnormally expressed. A *221*At-labelled mGluR1 inhibitor, *221*At-AITM, induces senescence of tumor cells and exerts antitumor effects in multiple tumors [229]. In addition, combination therapy with PI3K/mTOR inhibitors and HER2 or mGluR1 inhibitors efficiently decreases tumor growth in PTEN wild-type-PI3K/AKT mutant prostate cancer [230]. In the cerebral microenvironment, lung cancer cells are dependent on mGluR1 signaling, triggered by astrocytes through the Wnt-5a/prickle planar cell polarity protein 1/RE1 silencing transcription factor axis. Furthermore, mGluR1 facilitates the stabilization of EGFR, promoting brain metastasis [231]. Additionally, the activation of sirtuin 1 in the spinal cord by SRT1720 downregulates mGluR1/5 expression, alleviating bone cancer pain [232, 233]. Overexpression of mGluR1 also enhances melanoma progression through angiogenic signaling. Downstream of mGluR1, the AKT-mTOR-HIF pathway increases the concentrations of IL-8 and VEGF, leading to abundant blood vessels and tumor proliferation [234]. Riluzole can prevent tumor growth by inhibiting glutamate release in a Phase II trial in advanced melanoma [235].

NMDAR are expressed in different tumors and play a dual role in cancer development [236, 237]. Downregulation of the NMDAR2B subunit has been detected in esophageal cancer, gastric cancer, and non-small cell carcinoma [238–240]. Acting as a promoter of tumorigenesis, the activation of the NMDAR, the calcium-independent mitogen-activated protein kinase (MAPK) pathway, and the calcium-dependent calmodulin kinase (CaMK) pathway all contribute to the activation of the cAMP-responsive element-binding (CREB) transcription factor [241, 242]. In combinatorial CRISPR-Cas9 screening, the NMDAR antagonist ifenprodil synergized with sorafenib downregulated genes in WNT signaling and stemness and decreased the self-renewal ability of HCC cells [243]. Additionally, CREB upregulates the proto-oncogene c-Fos in a DNA double-strand-breaking manner. Breaking strands accelerate the transcription of early response genes and are recognized as the cause of tumorigenesis [244–246]. Li et al. provided evidence that glutamate from nerve cells causes calcium influx into PDAC. Furthermore, NMDAR-activated Ca^{2+}-dependent protein kinase CaMKII/ERK-MAPK pathway and METTL3 mRNA transcription were upregulated, and hexokinase 2 expression was subsequently upregulated by N6-methyladenosine modification, which improved PDAC cells' glycolysis and promoted perineural invasion [247]. Activated T cells suppress MDSCs through the JNK-NMDAR-ARG-1 pathway, which is attenuated by the NMDAR inhibitor, MK801 [248]. Similarly, NMDAR activation enhances the immunosuppressive activity of TAMs by triggering calcium influx and reactive oxygen species (ROS) production. Single-cell RNA sequencing showed that MK801, memantine, and magnesium blocked NMDAR ability and altered TAM phenotypes, which induced T cell and NK cell-mediated antitumor immunity [24] (Fig. 3, Table 3).

Serotonin (5-hydroxytryptamine, 5-HT)

Derived from tryptophan, 5-HT is a key neurotransmitter in the CNS, impacting the nervous system, gastrointestinal function, cancer initiation, and immune response in an autocrine or paracrine fashion [249–255]. 5-HT functions are primarily achieved by activating 5-HT receptors (HTRs), including 15 distinct subtypes 5HTR1–7 and serotonin transporter (SERT) [256]. The 5-HT receptors 1A, 1B, 2B, and 7 are expressed in HCC [257–260], in which 5-HTR1B and 5-HTR2B induce cancer cell proliferation and drug resistance through Notch signaling and autophagy [261]. In prostate cancer, 5-HTR 1A, 2B, and 4 have been observed, and antagonists of these receptors inhibit the proliferation of cancer cells [262, 263]. Subtypes of the 5-HTRs has been found in breast cancer [264], colon cancer [265, 266], pancreatic cancer [267], gastric cancer [268], ovary cancer [269],and lung cancer [270, 271]. Activated downstream pathways, including the adenylyl cyclase, MAPK, and PI3K/Akt pathways, promote cancer cell proliferation and inhibit apoptosis [252]. Notably, 5-HTRs play multiple roles in regulating immune responses. For instance, serotonylation of GAPDH Q262 induces $CD8^+$ T cell glycolytic metabolism, which activates antitumor immunity [272]. Additionally, 8-OH-DPAT functions as a 5-HTR_{1A} agonist that increases NK cells cytotoxicity [273]. The 5-HTR_{1A} antagonist (+), WAY 100135, inhibited B cell proliferation effect [274]. In summary, agonists and antagonists of 5-HTRs that participate in the regulation of immune cells provide new information on immune therapy [252] (Fig. 3, Table 3).

Gamma-aminobutyric acid

GABA, a non-proteinogenic amino acid, is produced from the excitatory neurotransmitter glutamate through the action of glutamic acid decarboxylase and is found in the brain, spinal cord, and tumors [275–277]. As a major inhibitory neurotransmitter, GABA regulates neuronal development, synaptic transmission, prevention of depression, and pain sensation through the ionotropic $GABA_A$ and $GABA_C$ receptors and the G protein-coupled $GABA_B$ receptor [278].

Irregular GABA levels have been associated with poor prognosis, as the $GABA_B$ receptor, activated by GABA, fosters β-catenin signaling, which in turn boosts tumor growth and curbs the infiltration of $CD8^+$ T cells within tumors. Targeting glutamate decarboxylase 1 or $GABA_B$ receptors can increase sensitivity to anti-PD-1 (programed death-1) immune checkpoint blockade therapy [276]. In PDAC, the expression of the GABA type A receptor pi subunit (GABRP) increases in tumor tissues. GABRP promoted Ca^{2+} entry by interacting with KCNN4, which activated nuclear factor κB signaling, leading to macrophage infiltration in a GABA-independent manner [279]. GABA inhibits electrical activity in melanoma and keratinocyte coculture systems. Blocking GABA synthesis decreased melanoma initiation [280]. Bao et al. reported that sleep deprivation increases peripheral blood GABA levels, which induces colon cancer cell proliferation and migration [281]. The delta subunit of the GABAA receptor is activated by overexpression of glutamic pyruvate transaminase (GPT2), which increases the GABA content. Moreover, activation of $GABA_A$-R-PKC-CREB signaling leads to the upregulation of PODXL, MMP3, and MMP9, which accelerates breast cancer metastasis [22]. GABA-targeted treatments have gained attention in cancer co-adjuvant therapy [282]. Baclofen, which functions as a $GABA_B$-R agonist, has been approved for clinical use [283, 284] and increases p-ERK1/2 levels in cerebellar neurons [285]. It can also induce chondrosarcoma cell metastasis, while the $GABA_B$-R antagonist CGP inhibits the G1/S cell cycle checkpoint and induces apoptotic pathways by inhibiting the MAPK and PI3K/AKT/mTOR signaling pathway [286]. GABA is also synthesized and secreted by activated B and plasma cells, which inhibit $CD8^+$ T cell killer function. Furthermore, the lack of glutamate decarboxylase 67, the GABA-generating enzyme, improves the antitumor response [287] (Fig. 3, Table 3).

Neurotrophins

Neurotrophins, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin 3 (NT3), play a vital role in nervous system development, as well as in learning, memory, and behavioral processes [288, 289]. The tropomyosin receptor kinase (Trk) family includes TrkA, TrkB, and TrkC, which have high affinities for NGF, BDNF, and NT3, respectively [290, 291]. In addition, paracrine and autocrine neurotrophins bind directly to Trks and activate downstream signaling pathways, including PI3K/AKT, MAPK, PLCγ/PKC pathways associated with cancer proliferation, angiogenesis, metastasis, and chemoresistance [291, 292]. Trks are recognized as oncogenes in tumors, and TrkB and TrkC regulate apoptosis in tumor cells [293, 294].

Autocrine NGF-activated TrkA on melanoma cells decreased interferon γ signaling, leading to T and NK cell exclusion. The TrkA inhibitor larotrectinib can reverse the suppression of the tumor immune microenvironment, thereby suppressing tumor progression [295]. In bone metastatic prostate cancer, Fbxo22 ubiquitinates Krueppel-like factor 4, which affects the NGF/TrkA axis by repressing NGF transcription, leading to downregulation of bone metastases and macrophage M2 polarization [296]. Moreover, mice with myocardial infarction exhibited increased tumor progression caused by elevated levels of NGF, which phosphorylated TrkA and activated the PI3K/AKT signaling pathway. The inhibitor GW441756, which blocks TrkA, inhibits downstream signaling and tumor progression [297]. In colorectal cancer, noradrenaline and NGF formed a positive loop and accelerated cancer progression through ADRA2A/Gi-mediated activation of YAP and PI3K/AKT pathway [298].

The BDNF/TrkB pathway enhances cancer proliferation, invasion, and migration and may be a potential therapeutic target in HCC and ovarian cancer [293, 299, 300]. Research by Jin et al. showed that lactate secreted by gastric cancer (GC) cells leads to the induction of cancer-associated fibroblasts (CAFs). They also discovered that an increase in BDNF from CAFs strengthens the TrkB-Nrf2 pathway in GC cells, which in turn reduces the apoptosis and reactive oxygen species caused by anlotinib, contributing to GC cells' acquired resistance to anlotinib [301]. Conversely, BDNF-expressing neurons in the hypothalamus decreased leptin levels through sympathoneural β-adrenergic signaling, thereby inhibiting melanoma and colon cancer model tumor growth and promoting remission [302].

In summary, neurotransmitters and neurotrophins play significant roles in cancer progression. Dopamine receptors influence tumor growth and immune responses, with receptor agonists and antagonists showing potential therapeutic effects. Glutamate receptors are involved in various cancers, with some acting as tumor promoters. Serotonin receptors are expressed in multiple cancers and modulate immune responses. GABA affects tumor proliferation and immune cell function, with potential for adjuvant therapy. Neurotrophins and their receptors are linked to cancer development, offering therapeutic targets (Table 3).

The impact of the nervous system in the tumor immune microenvironment

Sensory fibers and the tumor immune microenvironment

The calcitonin gene-related peptide (CGRP) and substance P, which are released from peripheral nerve fibers [303], have been shown to be associated with the sensing and regulation of the immune response

[304–306]. CGRP is a significant neurotransmitter involved in inflammation via the RAMP1 signaling pathway [307]. In addition, CGRP-knockout mice showed a significant reduction in tumor volume compared to WT mice. CGRP-knockout mice have a higher content of tumor-infiltrating $CD4^+$ T cells, $CD8^+$ T cells, and $NK1.1^+$ NK cells [308, 309]. These results demonstrate that CGRP modulates tumor progression in the immune microenvironment and may be a therapeutic target in cancer (Fig. 4, Table 4).

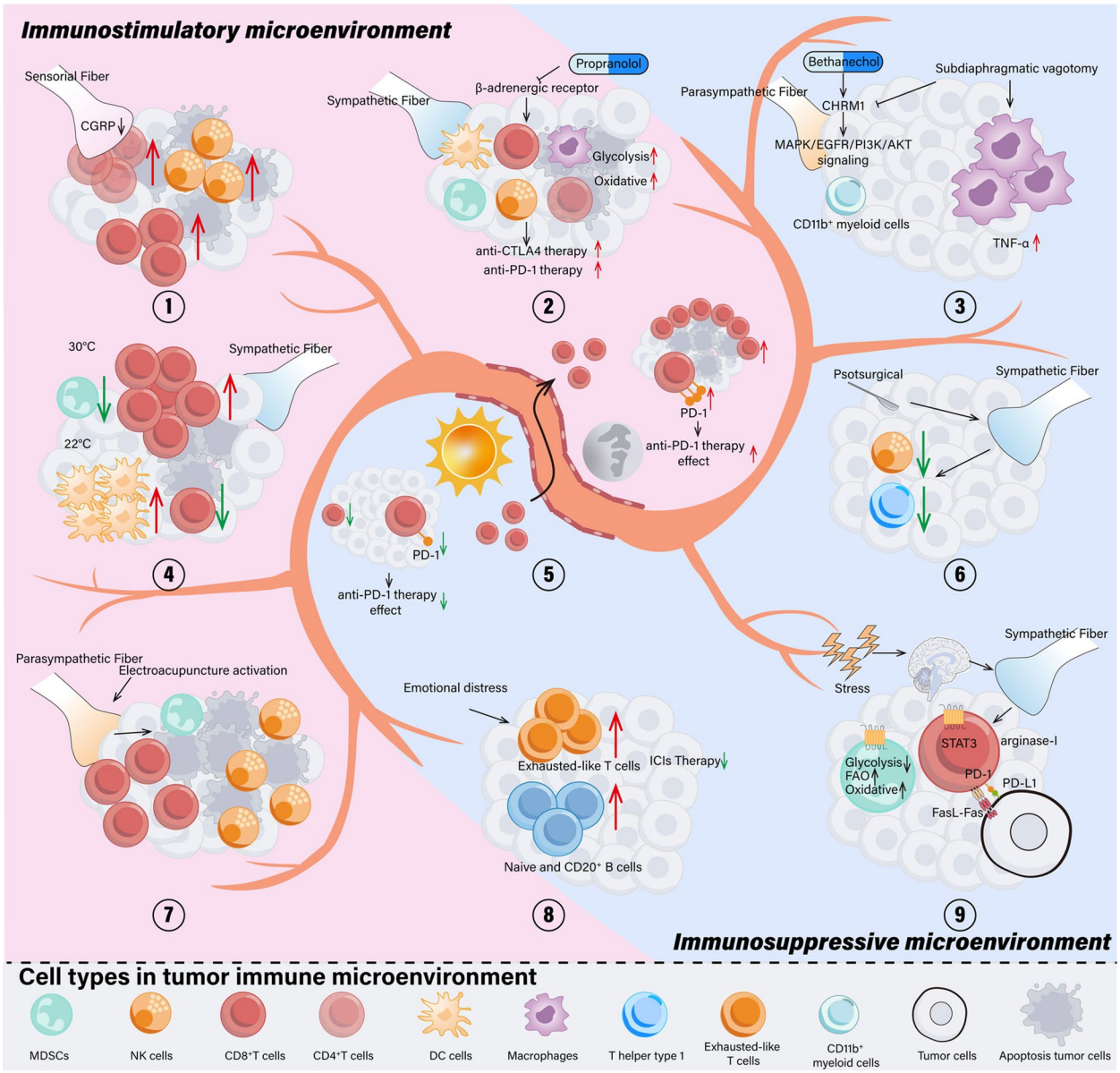

Fig. 4 The impact of the nervous system on tumor immune microenvironment. The relationship between nervous system including sensory fibers, sympathetic nervous system, parasympathetic nervous system and neurological functions with tumor immune microenvironment (TIME). (1) Calcitonin gene-related peptide (CGRP) modulate TIME. (2) Propranolol, by inhibiting the β-adrenergic receptor, has been shown to augment the therapeutic effectiveness of both anti-CTLA4 and anti-PD-1 immunotherapies. (3) Subdiaphragmatic vagotomy contributes to TIME. (4) Temperature contributes to TIME through sympathetic fiber. (5) Circadian clock associates with leukocyte infiltration of tumors controlled by endothelial cells. (6) Postsurgical caused stress condition in TIME. (7) Electroacupuncture activation of the vagus nerve affects TIME. (8) Emotional distress affects exhausted-like T cells and naïve B cells which relate with ICIs therapy efficiency. (9) Stress induced activation of β-adrenergic receptor signaling affects TIME

Table 4 External stimulus induced tumor immune microenvironment

Cancer Type	Immune Cell Type	External stimulus	Mechanism of Impact on Tumor Microenvironment	References
Colorectal cancer	Memory T cells	Vagus nerve modulates memory T cells	Vagal nerve mediates splenic secretion of TFF2, suppressing MDSCs expansion	[180]
Oral squamous cell carcinoma	$CD4^+$ T cells, $CD8^+$ T cells, NK cells	CGRP-knockout; Chronic adrenergic stress	Reduction in tumor volume; Suppressed $CD8^+$ T cells stimulation	[308, 309, 318]
Pan-cancer	MDSCs	Stress induced β2-adrenergic receptor signaling	β2-adrenergic signaling suppresses T cell proliferation via STAT3 phosphorylation and Fas-FasL interaction	[312]
Pan-cancer	MDSCs, DCs, $CD8^+$ T cells	Stress from temperature	High temperature reduces MDSCs, enhances $CD11b^+$ myeloid cell and plasmacytoid DCs, improving $CD8^+$ T cell activation	[314, 315]
Pan-cancer	NK cells	Surgery induced stress	Stress conditions mediate NK cell suppression	[316]
Lung metastasis	T cells, neutrophil	Chronic stress	Reduction of T cell infiltration and increasing NET formation led to lung metastasis	[320]
Colorectal cancer	T cell, MDSCs	Propranolol blocked β2-adrenergic receptor signaling	Increased T cell infiltration and reduced MDSCs infiltration which enhanced anti-CTLA4 therapy	[322]
Breast cancer	Myeloid Cells	Vagus nerve activation regulates myeloid cells	Increased the abundant of $CD8^+$ T cells and NK cells and inhibited the accumulation of MDSCs	[324]
Pancreatic cancer	Myeloid Cells	Parasympathetic signaling	Muscarinic signaling via CHRM1 regulates $CD11b^+$ myeloid cells, TNFα level, and cancer stem cells	[325]
Non-small-cell lung cancer	$CD8^+$ T Cells	Emotional distress impacts $CD8^+$ T cells	Emotional distress is associated with lower objective response rate in immune checkpoint inhibitors therapy	[327]
Pan-cancer	$CD4^+$ T Cells, $CD8^+$ T Cells, NK cells	Circadian rhythm	Circadian differences affected $CD4^+$ and $CD8^+$ T cells, $NK1.1^+$ cells, $CD11b^+$ $Ly6C^+$ cells, $CD11c^+$ $MHCII^+$ and $CD19^+$ cells which controlled by endothelial cells which affected CAR-T and anti-PD 1 therapy	[333, 334]

Sympathetic nervous system in the tumor immune microenvironment

Stress activates the SNS and HPA axes, resulting in the activation of adrenergic and glucocorticoid receptors [310, 311]. However, the crosstalk between β- adrenergic signaling and tumor immune microenvironment (TIME) remains debatable. The β2-adrenergic receptor signaling affected MDSCs frequency in tumors and the expression of arginase-I and PD-L1, which suppressed the proliferation of T cells through STAT3 phosphorylation and Fas-FasL interaction [312]. β2-adrenergic receptor stress pathway also performed its immune suppressive role in modulating MDSCs metabolism. The β2-adrenergic receptor signaling downregulated glycolysis and upregulated oxidative phosphorylation and FAO, which impeded antitumor immunity [313].

Kokolus et al. observed that tumors exhibited reduced volume and weight at room temperature (22 °C) as opposed to thermoneutral conditions (30 °C), a reduction attributed to a decrease in MDSCs and $CD11b^+$ myeloid cells, and an increase in plasmacytoid DCs at standard temperature. Consequently, the group maintained at thermoneutral temperature displayed a higher frequency of activated $CD8^+$T cells and a lower presence of immunosuppressive MDSCs within the TIME [314, 315]..

Surgery can cause stress and mediate NK cells suppression [316]. Moreover, in postoperative F344 rats harboring mammary adenocarcinoma and C57BL/6 rats bearing melanoma, there was a modification in the cytotoxic function of NK cells, along with a reduction in the secretion from Th1 cells [317]..

Chronic adrenergic stress of β2-adrenergic receptor signaling activation also suppressed immunotherapies

efficacy by decreasing IFNγ production and the cytolytic killing capacity of antigen-specific $CD8^+$ T cells. This alters DCs function and suppressed $CD8^+$ T cells stimulation [318]. Blocking β2-adrenergic receptor signaling reduces tumor progression by increasing cytokine production, which is accomplished by upregulating glycolysis and oxidative phosphorylation in tumor-infiltrating lymphocytes [319]. Moreover, T cell receptors could be suppressed by stress-induced β-adrenergic receptor signaling activation [319]. Furthermore, He et al. reported that chronic stress alters the lung environment by reducing T-cell infiltration and fibronectin accumulation and increasing neutrophil infiltration. Significantly, the formation of neutrophil extracellular traps (NETs) promotes lung metastasis, and this effect can be attenuated by deletion the glucocorticoid receptor specific to neutrophils [320]. Collectively, the β-adrenergic receptor antagonist propranolol is garnering more interest in the field of immunotherapy. In the context of metastatic melanoma, propranolol has been shown to enhance the effectiveness of anti-PD-1 immune checkpoint inhibitor therapy [321]. Additionally, propranolol has been found to boost the infiltration of T-cells and decrease the infiltration of MDSCs, thereby enhanced the efficacy of anti-CTLA4 therapy [322] (Fig. 4, Table 4).

Parasympathetic nervous system in the tumor immune microenvironment

To date, investigations of parasympathetic modulation and the immune system have focused mainly on crucial components of the vagus nerve [12, 146, 323]. Proinflammatory cytokines IL-1β and TNF-α in serum were regulated by electroacupuncture activation of the vagus nerve in breast tumor-bearing mice, which increased the abundance of $CD8^+$ T cells and NK cells along with inhibiting the accumulation of MDSCs [324]. In the orthotopic murine PDAC model, subdiaphragmatic vagotomy was observed to accelerate tumor growth, which was modulated by TAM secreting TNFα [179]. Another study in spontaneous formation of PDAC, subdiaphragmatic vagotomy or knockout of the muscarinic type 1 receptor (CHRM1) accelerated PDAC progression. Muscarinic signaling activated MAPK/EGFR and PI3K/AKT pathways via CHRM1, and cholinergic signaling regulated $CD11b^+$ myeloid cells, TNFα level, and cancer stem cells, therefore the systemic muscarinic agonist bethanechol suppressed tumorigenesis [325] (Fig. 4, Table 4). The vagal nerve also modulates memory T cells to suppress MDSC expansion by mediating the secretion of the splenic protein trefoil factor 2 (TFF2), an anti-inflammatory peptide. Furthermore, transgenic overexpression of TFF2, adenoviral transfer of TFF2, or transplantation of TFF2 expression into the bone marrow could attenuate colorectal tumorigenesis [180] (Fig. 2).

Neurological function in the tumor immune microenvironment

Emotional distress (ED), including depression or anxiety [326], is closely associated with NSCLC, hematologic malignancies, and ovarian tumors, and its impact on TIME has been evaluated [327–329]. Pre-diagnosis depression was observed in women with an increasing abundance of activated cytotoxic ($CD3^+CD8^+CD69^+$) and exhausted T cells ($CD3^+Lag3^+$) in the tumors. In high-grade serous carcinomas, depression is associated with naïve and memory B cells ($CD20^+$) [328]. In NSCLC, patients with ED, assessed using the Patient Health Questionnaire-9 and Generalized Anxiety Disorder 7-item scale, had a shorter median progression-free survival. In addition, ED is associated with a lower objective response rate in immune checkpoint inhibitor therapy [327].

The immune system is regulated by the circadian clock [52, 330–332]. DCs and $CD8^+$ T cells exert circadian antitumor functions through tumor draining lymph nodes (dLN) [333]. Wang et al. found that leukocyte infiltration of tumors performed a circadian pattern [334]. Specifically, circadian differences affect $CD4^+$ and $CD8^+$ T cells, $NK1.1^+$ cells, $CD11b^+$ $Ly6C^+$ cells, $CD11c^+$ $MHCII^+$ cells, and $CD19^+$ cells, which are controlled by endothelial cells [334]. Notably, human Chimeric antigen receptor (CAR) T cells demonstrated better therapeutic efficacy when the time of injection was adjusted to the evening. In $CD8^+$ T cells, both mRNA and protein levels of *Pdcd1* (encoding PD-1) peaked in the morning, indicating that the administration of anti-PD-1 in the evening caused better activation in tumor [334]. Fortin et al. used an intestine-specific knockout *Bmal1* (disrupting the circadian clock) and heterozygous deletion of *Apc* (initiating CRC) in a genetically engineered mouse model to identify circadian clock changes in the immune landscape via single-cell RNA sequencing. Cytotoxic $CD8^+$ T cells and PD-L1-expressing MDSCs showed a peak in abundance in a time-of-day manner [335]. Collectively, the efficacy of immune checkpoint inhibitors (ICIs) is affected by the circadian clock, demonstrating the optimal timing of ICI therapy.

In conclusion, the nervous system significantly impacts the TIME. Sensory fibers like CGRP and substance P regulate immune responses, with CGRP influencing tumor progression and potentially serving as a therapeutic target. The sympathetic nervous system (SNS), activated by stress, can suppress antitumor immunity through β-adrenergic signaling, affecting MDSCs and T cell proliferation. Parasympathetic activity, particularly via the

vagus nerve, modulates cytokines and immune cell populations, impacting tumor growth. Emotional distress and circadian rhythms also play roles in TIME, with implications for the timing and efficacy of immunotherapies (Fig. 4, Table 4).

Cancer neuroscience in cancer therapy

Optogenetic in cancer therapy

Light-sensitive proteins are employed to the optogenetic tools to cancer treatment which effector proteins to reversibly activate fundamental cellular functions without causing lasting effects [336–338]. Specific wavelengths of light can non-invasively stimulate the immune response, enhance oncolytic activity, and regulate cell signaling within tumor cells [339, 340]. Similarly, inserting an optogenetic probe rectally in mice that express channelrhodopsin-2 (ChR2) in tyrosine hydroxylase-containing cells stimulated colonic sympathetic nerve fibers. Local activation of sympathetic fibers reduces $CD45^+$ cell abundance and regulates immune cell extravasation, attenuating colonic inflammation [341]. The unique control of local sympathetic fibers and immune microenvironment may provide a new treatment strategy for cancer therapy. CAR T cell-based immunotherapies continue to face with safety issues stemming from complications like cytokine release syndrome and "on-target, off-tumor toxicity" [342, 343]. Nano-optogenetic engineering of CAR T cells are designed to remotely phototune T cell activation to accurately trigger the destruction of tumor cells which establish the safe limits of anti-cancer immunity to prevent the occurrence of harmful side effects [344, 345].

Neuromodulatory drugs in cancer therapy

Cancer neuroscience, which explores the use of nervous system-related drugs in cancer treatment, has emerged as a novel area of research and garnered increasing attention in recent years [26, 346]. Anti-NGF therapy, tanezumab, has been tested to reduce pain caused by bone metastases (NCT02609828) [347]. Moreover, the epileptic disorders drug valproate was used in RAS-mutated metastatic CRC (NCT04310176) [348].

In the realm of neuromodulation drugs, the antagonist or agonist for dopamine receptor 2/3, glutamate receptors, and β-adrenergic receptors has attracted increased attention [11, 26]. ONC201, also known as Dordaviprone, has been identified as an antagonist for the dopamine receptors DRD2 and DRD3. It is capable of penetrating the blood–brain barrier and inhibiting the pro-survival signaling pathways AKT-ERK [349–352]. It has been used in clinical trials for a variety of tumor types, including H3 K27M-mutant diffuse midline glioma (NCT02525692) [353, 354], neuroendocrine tumors (NCT03034200) [355] and endometrial cancer (NCT03394027) [356, 357]. In a Phase II study of ONC201 in patients with metastatic breast cancer and advanced endometrial carcinoma, ONC201 upregulated naïve cells and decreased subsets of effector memory cells among total peripheral $CD4^+$ T cells [357].

Therapeutic strategies using neuropsychiatric drugs have been developed based on the high levels of glutamate released into the synaptic cleft. AMPAR antagonists perampanel and talampanel (NCT00943826, NCT00689221, NCT00813943, and NCT00884741) decreased calcium-related cell division and increased cancer cell death by counteracting high levels of glutamate [125, 129]. Imipramine Blue (IB) inhibits the invasion of GBM, and the combination of nano-IB therapy with doxorubicin in chemotherapy can prolong survival [358]. Mechanistically, IB suppresses ROS generation mediated by the reduced form of nicotinamide adenine dinucleotide phosphate oxidase and modifies the expression of actin regulatory components [358]. Another study demonstrated that IB inhibited breast cancer growth by interacting with and inhibiting the proto-oncogene FoxM1, which affects homologous recombination-mediated DNA repair [359]. In the model causing anxiety and stress, glutamate release is triggered by the depolarization of synaptosomes in the PFC, while drugs for mood/anxiety disorders (fluoxetine, desipramine, venlafaxine, and agomelatine) can prevent the upregulation of glutamate release [360]. Moreover, tricyclic antidepressants, such as imipramine and desipramine, recognized for their ability to inhibit the reuptake of serotonin, might also eliminate excitatory postsynaptic potentials by inhibiting glutamate release in the PFC [361]. The β-adrenergic antagonist propranolol or carvedilol could reduce the pro-metastatic and invasive markers, enhancing the efficacy of cancer treatment and increasing the survival time in PDAC (NCT02944201), glioblastoma (NCT03861598), melanoma, breast cancer (NCT03861598 NCT02944201), and prostate cancer [321, 362–365]. The combination of propranolol and the anti-PD-1 checkpoint inhibitor pembrolizumab in metastatic melanoma showed promising antitumor activity in a Phase II trial (NCT03384836) [366]. The Phase III trial (NCT02362594) suggested β-adrenergic blockers improved the efficacy of pembrolizumab treatment, but did not have a prognostic effect [367]. Collectively, neuromodulatory drug combination therapies have broad prospects but still require further research (Table 5).

Conclusion and future perspectives

The interface between neuroscience and cancer progression has emerged as a burgeoning and complex field of scientific investigation with substantial implications for therapeutic development. We systematically reviewed

Table 5 Therapies targeting the tumor–nervous system axis

Cancer	Therapy	Target	Mechanism	Outcome	References
Bone metastases	Tanezumab	Anti-NGF	Improved pain and function in chronic pain conditions such as osteoarthritis and chronic low-back pain	Reduce pain caused by bone metastases	NCT02609828
RAS-mutated metastatic colorectal cancer	Valproate	Histone-deacetylase inhibitors	Regulation of different altered pathway in cancer, such as apoptosis, cell cycle, and DNA repair	Not reported	NCT04310176
H3 K27M-mutant diffuse midline glioma	ONC201	Antagonist of DRD2/3	Suppressed the pro-survival AKT-ERK pathway	8 of 12 patients alive at < 12 months median follow-up	NCT02525692
Neuroendocrine tumors	ONC201	Antagonist of DRD2/3	Suppressed the pro-survival AKT-ERK pathway	56% progressed	NCT03034200
Endometrial cancer	ONC201	Antagonist of DRD2/3	Upregulate naïve cells and decrease the subsets of effector memory cells	Acceptable safety profile	NCT03394027
Glioblastoma	Talampane	AMPAR antagonists	Decreased calcium-related cell division and increased cancer cell death	Improved overall survival compared with historical controls	NCT00943826, NCT00689221, NCT00813943, NCT00884741
PDAC	Carvedilol	β-adrenergic antagonist	Reduced the pro-metastatic and invasive markers	Enhanced the efficacy of cancer treatment and increased the survival time	NCT02944201
Glioblastoma	Carvedilol	β-adrenergic antagonist	Reduced the pro-metastatic and invasive markers	Increased the survival time	NCT03861598
Colorectal cancer	Propranolol, COX2 inhibitor	β-adrenergic antagonist	Inhibited by the non-selective β-blocker propranolol	No difference in recurrence	NCT00888797
Breast cancer	Propranolol, COX2 inhibitor	β-adrenergic antagonist	Inhibited by the non-selective β-blocker propranolol	Decreased pro-metastatic and invasive markers	NCT00502684
Breast cancer	Propranolol, chemotherapy	β-adrenergic antagonist	Inhibited by the non-selective β-blocker propranolol	Not reported	NCT01847001
Melanoma	Propranolol	β-adrenergic antagonist	Combination of propranolol and the anti-PD1 checkpoint inhibitor pembrolizumab	No dose-limiting toxicity; objective response rate 78%; improved efficacy of pembrolizumab treatment	NCT03384836, NCT02362594

the role of neuroscience in the regulation of tumor initiation, progression, and metastasis in different malignancies. We observed that cerebral regions which regulate various neurological functions are involved in tumor progression in multiple ways. The hypothalamus, with its subdivisions, such as the PVN, which governs the stress response, particularly regulates the downstream of the HPA axis and the SAS and has been shown to play a key role in mediating the impact of stress on tumorigenesis and the functionality of the immune system [35, 42]. The circadian rhythm modulated by the SCN located in the anterior and lateral hypothalamus regulates wakefulness and plays a significant role in tumorigenesis, progression, and metastasis [60, 66]. Furthermore, the hippocampus, PFC, amygdala, and VTA have been studied for their contributions to neurobehavioral sequelae associated with cancer [112, 113]. Synapse input and neurotransmitters, including dopamine, glutamate, serotonin, GABA, and neurotrophins, have been recognized for their significant influence on the behavior of tumor cells and the function of immune cells, and their dysregulation within the tumor microenvironment has been implicated in modulating immune responses and promoting tumor growth [23, 241, 272, 287, 302]. Sensory fibers, the autonomic nervous system (SNS and PNS), and neurological functions, such as ED and dysregulation of the circadian clock, have been examined for their dual influences on cancer onset and progression, and modulating the TIME presents a significant opportunity for the discovery of novel therapeutic targets [312, 327, 333].

Although medications that alter abnormal neurological functions and psychoactive drugs that interfere with neural signal transmission have been widely used in clinical practice, the challenge is to uncover the precise neuroimmune–tumor interactions that promote or impede tumor progression. A more profound understanding of the mechanisms by which neurotransmitters and neurotrophic factors contribute to the tumor microenvironment will be essential. The role of the autonomic nervous system in modulating the immune response to cancer presents a significant opportunity for the discovery of novel therapeutic targets. The development of novel neuromodulatory drugs and their integration into immunotherapeutic strategies will be a critical focus for future research. Currently, preclinical studies have investigated the DRD2/3 antagonist: ONC201, AMPAR antagonist: perampanel or talampanel, β-adrenergic antagonist: propranolol or carvedilol [353, 357, 365]. Both of these inhibitors hamper tumor development and promotes antitumor immune response effects. Additionally, the combination of neuromodulation drugs and ICIs improves the efficacy of immunotherapy [366]. Therefore, it is imperative to identify compounds capable of specifically targeting neural pathways that contribute to cancer progression without altering physiological homeostasis. Moreover, the prospect of personalized medicine in neuro-oncology, based on an individual's unique neuroimmune profile, introduces precision medicine for cancer therapy.

In summary, the integration of neuroscience and oncology requires concerted efforts across multiple disciplines, including neurobiology, immunology, and cancer research. With sustained research and clinical innovation, the future of cancer neuroscience holds promise for delivering more effective and personalized cancer treatments, thereby enhancing patient outcomes and ultimately redefining our approach to combating cancer. Therefore, this field of investigation will refine our understanding of the pathophysiological relationship between the CNS, ANS, TIME, and cancer development and pave the way for transformative therapeutics that harness neuroscience mechanisms to combat tumorigenesis and metastasis.

Abbreviations

6-OHDA	6-Hydroxydopamine
Ach	Acetylcholine
ACSL1	Acyl-CoA synthetase 1
ALL	Acute lymphoblastic leukemia
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionate receptor
B2BM	Breast to brain metastasis
ChR2	Channelrhodopsin-2
CKIε	Casein kinase Iε
CRC	Colorectal cancer
CRD	Circadian rhythm disturbance
Cry	Cryptochrome
DA	Dopamine
DCs	Dendritic cells
DEN	Diethylnitrosamine
DRD1	Dopamine D1 receptors
dLN	Tumor draining lymph node
ED	Emotional distress
EGFR	Epidermal growth factor receptor
FAO	Fatty acid oxidation
GABA	Gamma-aminobutyric acid
GABRP	Gamma-aminobutyric acid type A receptor pi subunit
GAD1	Glutamate decarboxylase 1
GAD67	Glutamate decarboxylase 67
GBM	Glioblastoma
GC	Gastric cancer
G-CSF	Granulocyte colony-stimulating factor
HK2	Hexokinase 2
HTRs	5-HT receptors
IARC	International Agency for Research on Cancer
IB	Imipramine Blue
IFNγ	Interferon γ
iGluR	Inotropic glutamate receptor
m6A	N6-methyladenosine
mGluR	Metabotropic glutamate receptor
KR	Kainate receptor
KLF4	Krueppel-like factor 4
LH	Lateral hypothalamus
M3 receptor	Muscarinic acetylcholine receptor 3
MDSCs	Myeloid-derived suppressor cells
NADPH	Nicotinamide adenine dinucleotide phosphate
NETs	Neutrophil extracellular traps
NGF	Nerve growth factor

NMDAR	N-methyl-d-aspartate receptor
NSCLC	Non-small cell lung cancer
NT3	Neurotrophin 3
PD-1	Programed death-1
PD-L1	Programed death ligand-1
PFC	Prefrontal cortex
PNS	Parasympathetic nervous system
PRICKLE1	Planar cell polarity protein 1
PVN	Paraventricular nucleus
REST	RE1 silencing transcription factor
ROS	Reactive oxygen species
S4F	Semaphorin 4F
SAS	Sympathetic-adrenal system
SCN	Suprachiasmatic nucleus
SERT	Serotonin transporter
SIRT1	Sirtuin 1
SNS	Sympathetic nervous system
ST	Standard temperature
SVZ	Subventricular zone
TFF2	Trefoil factor 2
TH	Tyrosine hydroxylase
TIL	Tumor-infiltrating lymphocytes
T-cells	T-cell receptor
TKIs	Tyrosine kinase inhibitors
TME	Tumor microenvironment
TIME	Tumor immune microenvironment
TT	Thermoneutral temperature
Trk	Tropomyosin receptor kinase
VIP	Vasoactive intestinal polypeptide
VTA	Ventral tegmental area

Acknowledgements
We would like to extend our sincere gratitude to Hangzhou Lingkai Science and Technology Culture Co. LTD for their invaluable guidance and support in the preparation of our graphical representations.

Authors' contributions
Qibo Huang, Bai Hu and Ping Zhang contribute to acquisition, write original draft and figure drawing. Xiaoping Chen, Bixiang Zhang and Zhouping Tang make the conceptualization. Junnan Liang drafted the work. Qibo Huang, Ye Yuan and Shiwei Yue substantively revised it. All authors read and approved the final manuscript.

Funding
This work was supported by the Major Program (JD) of Hubei Province (2023BAA005), the National Natural Science Foundation of China (92148206 and 82071330), the Key Research and Development Program of Wuhan (2024020702030123), the Young Scientists Fund of the National Natural Science Foundation of China (82303185) and Huazhong University of Science and Technology (2023JCYJ033).

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

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 21 November 2024 Accepted: 26 December 2024
Published online: 17 January 2025

References

1. Sousa AMM, Meyer KA, Santpere G, Gulden FO, Sestan N. Evolution of the Human Nervous System Function, Structure, and Development. Cell. 2017;170:226–47. https://doi.org/10.1016/j.cell.2017.06.036.
2. Black IB, et al. Biochemistry of information storage in the nervous system. Science. 1987;236:1263–8. https://doi.org/10.1126/science.2884727.
3. Bissell MJ, Hines WC. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat Med. 2011;17:320–9. https://doi.org/10.1038/nm.2328.
4. Paget S. The distribution of secondary growths in cancer of the breast 1889. Cancer Metastasis Rev. 1989;8:98–101.
5. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971;285:1182–6. https://doi.org/10.1056/NEJM197111182852108.
6. Monje M, et al. Roadmap for the Emerging Field of Cancer Neuroscience. Cell. 2020;181:219–22. https://doi.org/10.1016/j.cell.2020.03.034.
7. Boilly B, Faulkner S, Jobling P, Hondermarck H. Nerve dependence: from regeneration to cancer. Cancer Cell. 2017;31:342–54. https://doi.org/10.1016/j.ccell.2017.02.005.
8. Hayakawa Y, et al. nerve growth factor promotes gastric tumorigenesis through aberrant cholinergic signaling. Cancer Cell. 2017;31:21–34. https://doi.org/10.1016/j.ccell.2016.11.005.
9. Stopczynski RE, et al. Neuroplastic changes occur early in the development of pancreatic ductal adenocarcinoma. Cancer Res. 2014;74:1718–27. https://doi.org/10.1158/0008-5472.CAN-13-2050.
10. Ruan J, Yao Y. Behavioral tests in rodent models of stroke. Brain Hemorrhages 1. 2020;171–184. https://doi.org/10.1016/j.hest.2020.09.001
11. Magnon C, Hondermarck H. The neural addiction of cancer. Nat Rev Cancer. 2023;23:317–34. https://doi.org/10.1038/s41568-023-00556-8.
12. Schiller M, Ben-Shaanan TL, Rolls A. Neuronal regulation of immunity: why, how and where? Nat Rev Immunol. 2021;21:20–36. https://doi.org/10.1038/s41577-020-0387-1.
13. Miller WL. The Hypothalamic-Pituitary-Adrenal Axis: A Brief History. Horm Res Paediatr. 2018;89:212–23. https://doi.org/10.1159/000487755.
14. Noble RE. Diagnosis of stress. Metabolism. 2002;51:37–9. https://doi.org/10.1053/meta.2002.33190.
15. Wang H, et al. Time-restricted feeding shifts the skin circadian clock and alters UVB-induced DNA damage. Cell Rep. 2017;20:061–1072. https://doi.org/10.1016/j.celrep.2017.07.022.
16. Liu Q, et al. A clock-dependent brake for rhythmic arousal in the dorsomedial hypothalamus. Nat Commun. 2023;14:6381. https://doi.org/10.1038/s41467-023-41877-4.
17. Cui Z, et al. Maternal circadian rhythm disruption affects neonatal inflammation via metabolic reprograming of myeloid cells. Nat Metab. 2024;6:899–913. https://doi.org/10.1038/s42255-024-01021-y.
18. Liu Q, et al. Coordination between circadian neural circuit and intracellular molecular clock ensures rhythmic activation of adult neural stem cells. Proc Natl Acad Sci U S A. 2024;121:e2318030121. https://doi.org/10.1073/pnas.2318030121.
19. Siebenga FF, et al. Emotion recognition in relation to tumor characteristics in patients with low-grade glioma. Neuro Oncol. 2024;26:528–37. https://doi.org/10.1093/neuonc/noad209.
20. Mancusi R, Monje M. The neuroscience of cancer. Nature. 2023;618:467–79. https://doi.org/10.1038/s41586-023-05968-y.
21. Zahalka AH, Frenette PS. Nerves in cancer. Nat Rev Cancer. 2020;20:143–57. https://doi.org/10.1038/s41568-019-0237-2.
22. Li N, et al. The delta subunit of the GABA(A) receptor is necessary for the GPT2-promoted breast cancer metastasis. Theranostics. 2023;13:1355–69. https://doi.org/10.7150/thno.80544.
23. Leng ZG, et al. Activation of DRD5 (dopamine receptor D5) inhibits tumor growth by autophagic cell death. Autophagy. 2017;13:1404–19. https://doi.org/10.1080/15548627.2017.1328347.
24. Yuan D, et al. NMDAR antagonists suppress tumor progression by regulating tumor-associated macrophages. Proc Natl Acad Sci U S A. 2023;120:e2302126120. https://doi.org/10.1073/pnas.2302126120.
25. Jacobson A, Yang D, Vella M, Chiu IM. The intestinal neuro-immune axis: crosstalk between neurons, immune cells, and microbes. Mucosal Immunol. 2021;14:555–65. https://doi.org/10.1038/s41385-020-00368-1.

26. Shi DD, et al. Therapeutic avenues for cancer neuroscience: translational frontiers and clinical opportunities. Lancet Oncol. 2022;23:e62–74. https://doi.org/10.1016/S1470-2045(21)00596-9.
27. Hanahan D, Monje M. Cancer hallmarks intersect with neuroscience in the tumor microenvironment. Cancer Cell. 2023;41:573–80. https://doi.org/10.1016/j.ccell.2023.02.012.
28. Silverman DA, et al. Cancer-Associated Neurogenesis and Nerve-Cancer Cross-talk. Cancer Res. 2021;81:1431–40. https://doi.org/10.1158/0008-5472.CAN-20-2793.
29. Khanmammadova N, Islam S, Sharma P, Amit M. Neuro-immune interactions and immuno-oncology. *Trends*. Cancer. 2023;9:636–49. https://doi.org/10.1016/j.trecan.2023.05.002.
30. Gao C, et al. Two genetically, anatomically and functionally distinct cell types segregate across anteroposterior axis of paraventricular thalamus. Nat Neurosci. 2020;23:217–28. https://doi.org/10.1038/s41593-019-0572-3.
31. Daviu N, et al. Paraventricular nucleus CRH neurons encode stress controllability and regulate defensive behavior selection. Nat Neurosci. 2020;23:398–410. https://doi.org/10.1038/s41593-020-0591-0.
32. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol. 2004;5:617–25. https://doi.org/10.1016/S1470-2045(04)01597-9.
33. Visintainer MA, Volpicelli JR, Seligman ME. Tumor rejection in rats after inescapable or escapable shock. Science. 1982;216:437–9.
34. Saul AN, et al. Chronic stress and susceptibility to skin cancer. J Natl Cancer Inst. 2005;97:1760–7. https://doi.org/10.1093/jnci/dji401.
35. Dai S, et al. Chronic Stress Promotes Cancer Development. Front Oncol. 2020;10:1492. https://doi.org/10.3389/fonc.2020.01492.
36. Leistner C, Menke A. Hypothalamic-pituitary-adrenal axis and stress. Handb Clin Neurol. 2020;175:55–64. https://doi.org/10.1016/B978-0-444-64123-6.00004-7.
37. Cui B, et al. Cancer and stress: NextGen strategies. Brain Behav Immun. 2021;93:368–83. https://doi.org/10.1016/j.bbi.2020.11.005.
38. Scherholz ML, Schlesinger N, Androulakis IP. Chronopharmacology of glucocorticoids. Adv Drug Deliv Rev. 2019;151–152:245–61. https://doi.org/10.1016/j.addr.2019.02.004.
39. Arlt W, Stewart PM. Adrenal corticosteroid biosynthesis, metabolism, and action. Endocrinol Metab Clin North Am. 2005;34:293–313. https://doi.org/10.1016/j.ecl.2005.01.002.
40. Beltrametti SP, Ianniello A, Ricci C. Chronotherapy with low-dose modified-release prednisone for the management of rheumatoid arthritis: a review. Ther Clin Risk Manag. 2016;12:1763–76. https://doi.org/10.2147/TCRM.S112685.
41. Obradovic MMS, et al. Glucocorticoids promote breast cancer metastasis. Nature. 2019;567:540–4. https://doi.org/10.1038/s41586-019-1019-4.
42. Diamantopoulou Z, et al. The metastatic spread of breast cancer accelerates during sleep. Nature. 2022;607:156–62. https://doi.org/10.1038/s41586-022-04875-y.
43. Bernabe DG. catecholamines mediate psychologic stress-induced cancer progression. Cancer Res. 2021;81:5144–6. https://doi.org/10.1158/0008-5472.CAN-21-3077.
44. Cui B, et al. Stress-induced epinephrine enhances lactate dehydrogenase A and promotes breast cancer stem-like cells. J Clin Invest. 2019;129:1030–46. https://doi.org/10.1172/JCI121685.
45. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338:171–9. https://doi.org/10.1056/NEJM199801153380307.
46. Thaker PH, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nat Med. 2006;12:939–44. https://doi.org/10.1038/nm1447.
47. Herman JP. Regulation of hypothalamo-pituitary-adrenocortical responses to stressors by the nucleus of the solitary tract/dorsal vagal complex. Cell Mol Neurobiol. 2018;38:25–35. https://doi.org/10.1007/s10571-017-0543-8.
48. Peters LJ, Kelly H. The influence of stress and stress hormones on the transplantability of a non-immunogenic syngeneic murine tumor. Cancer 1977;39:1482–1488. https://doi.org/10.1002/1097-0142(197704)39:4<1482::aid-cncr2820390420>3.0.co;2-p
49. Straif K, et al. Carcinogenicity of shift-work, painting, and fire-fighting. Lancet Oncol. 2007;8:1065–6. https://doi.org/10.1016/S1470-2045(07)70373-X.
50. Huang W, Ramsey KM, Marcheva B, Bass J. Circadian rhythms, sleep, and metabolism. J Clin Invest. 2011;121:2133–41. https://doi.org/10.1172/JCI46043.
51. Zhou L, et al. Circadian rhythms and cancers: the intrinsic links and therapeutic potentials. J Hematol Oncol. 2022;15:21. https://doi.org/10.1186/s13045-022-01238-y.
52. Wang Y, et al. Circadian regulation of cancer stem cells and the tumor microenvironment during metastasis. Nat Cancer. 2024;5:546–56. https://doi.org/10.1038/s43018-024-00759-4.
53. Hastings MH, Maywood ES, Brancaccio M. Generation of circadian rhythms in the suprachiasmatic nucleus. Nat Rev Neurosci. 2018;19:453–69. https://doi.org/10.1038/s41583-018-0026-z.
54. Rosenwasser AM, Turek FW. Neurobiology of Circadian Rhythm Regulation. Sleep Med Clin. 2015;10:403–12. https://doi.org/10.1016/j.jsmc.2015.08.003.
55. Ralph MR, Foster RG, Davis FC, Menaker M. Transplanted suprachiasmatic nucleus determines circadian period. Science. 1990;247(4945):975–8. https://doi.org/10.1126/science.2305266.
56. King VM, et al. A hVIPR transgene as a novel tool for the analysis of circadian function in the mouse suprachiasmatic nucleus. Eur J Neurosci. 2003;17:822–32. https://doi.org/10.1046/j.1460-9568.2003.02487.x.
57. Masri S, Sassone-Corsi P. The emerging link between cancer, metabolism, and circadian rhythms. Nat Med. 2018;24:1795–803. https://doi.org/10.1038/s41591-018-0271-8.
58. Hans Reinke GA. Crosstalk between metabolism and circadian clocks. Nat Rev Mol Cell Biol. 2019;20(4):227–41. https://doi.org/10.1038/s41580-018-0096-9.
59. Morgan MN, et al. The Cancer Clock Is (Not) Ticking: Links between Circadian Rhythms and Cancer. Clocks Sleep. 2019;1:435–58. https://doi.org/10.3390/clockssleep1040034.
60. Sulli G, Lam MT, Panda S. Interplay between Circadian Clock and Cancer: New Frontiers for Cancer Treatment. Trends Cancer. 2019;5(8):475–94. https://doi.org/10.1016/j.trecan.2019.07.002.
61. Chu LW, et al. Circadian genes and risk of prostate cancer in the prostate cancer prevention trial. Mol Carcinog. 2018;57:462–6. https://doi.org/10.1002/mc.22770.
62. Reszka E, Przybek M, Muurlink O, Peplonska B. Circadian gene variants and breast cancer. Cancer Lett. 2017;390:137–45. https://doi.org/10.1016/j.canlet.2017.01.012.
63. Innominato PF, et al. Circadian rest-activity rhythm as an objective biomarker of patient-reported outcomes in patients with advanced cancer. Cancer Med. 2018;7:4396–405. https://doi.org/10.1002/cam4.1711.
64. Van Dycke KC, et al. Chronically Alternating Light Cycles Increase Breast Cancer Risk in Mice. Curr Biol. 2015;25:1932–7. https://doi.org/10.1016/j.cub.2015.06.012.
65. Cadenas C, et al. Loss of circadian clock gene expression is associated with tumor progression in breast cancer. Cell Cycle. 2014;13:3282–91. https://doi.org/10.4161/15384101.2014.954454.
66. Papagiannakopoulos T, et al. Circadian Rhythm Disruption Promotes Lung Tumorigenesis. Cell Metab. 2016;24:324–31. https://doi.org/10.1016/j.cmet.2016.07.001.
67. Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. Epidemiology. 2007;18:182–3. https://doi.org/10.1097/01.ede.0000249519.33978.31.
68. O'Neill JS, Maywood ES, Chesham JE, Takahashi JS, Hastings MH. cAMP-dependent signaling as a core component of the mammalian circadian pacemaker. Science. 2008;320:949–53. https://doi.org/10.1126/science.1152506.
69. Dibner C, Schibler U, Albrecht U. The mammalian circadian timing system: organization and coordination of central and peripheral clocks. Annu Rev Physiol. 2010;72:517–49. https://doi.org/10.1146/annurev-physiol-021909-135821.
70. Joye DAM, et al. Somatostatin regulates central clock function and circadian responses to light. Proc Natl Acad Sci U S A. 2023;120:e2216820120. https://doi.org/10.1073/pnas.2216820120.
71. Shearman LP, et al. Interacting molecular loops in the mammalian circadian clock. Science. 2000;288:1013–9. https://doi.org/10.1126/science.288.5468.1013.
72. Kondratov RV, Shamanna RK, Kondratova AA, Gorbacheva VY, Antoch MP. Dual role of the CLOCK/BMAL1 circadian complex in transcriptional

regulation. FASEB J. 2006;20(3):530–2. https://doi.org/10.1096/fj.05-5321fje.
73. Haque SN, Booreddy SR, Welsh DK. Effects of BMAL1 Manipulation on the Brain's Master Circadian Clock and Behavior. Yale J Biol Med. 2019;92:251–8.
74. Akashi M, Tsuchiya Y, Yoshino T, Nishida E. Control of intracellular dynamics of mammalian period proteins by casein kinase I epsilon (CKIepsilon) and CKIdelta in cultured cells. Mol Cell Biol. 2002;22:1693–703. https://doi.org/10.1128/MCB.22.6.1693-1703.2002.
75. Vielhaber EL, Duricka D, Ullman KS, Virshup DM. Nuclear export of mammalian PERIOD proteins. J Biol Chem. 2001;276:45921–7. https://doi.org/10.1074/jbc.M107726200.
76. Schmalen I, et al. Interaction of circadian clock proteins CRY1 and PER2 is modulated by zinc binding and disulfide bond formation. Cell. 2014;157:1203–15. https://doi.org/10.1016/j.cell.2014.03.057.
77. Akashi M, et al. A positive role for PERIOD in mammalian circadian gene expression. Cell Rep. 2014;7:1056–64. https://doi.org/10.1016/j.celrep.2014.03.072.
78. Ikeda R, et al. REV-ERBalpha and REV-ERBbeta function as key factors regulating Mammalian Circadian Output. Sci Rep. 2019;9:10171. https://doi.org/10.1038/s41598-019-46656-0.
79. Duez H, Staels B. Rev-erb-alpha: an integrator of circadian rhythms and metabolism. J Appl Physiol. 1985;2009(107):1972–80. https://doi.org/10.1152/japplphysiol.00570.2009.
80. Jetten AM. Retinoid-related orphan receptors (RORs): critical roles in development, immunity, circadian rhythm, and cellular metabolism. Nucl Recept Signal. 2009;7:e003. https://doi.org/10.1621/nrs.07003.
81. Wood PA, et al. Period 2 mutation accelerates ApcMin/+ tumorigenesis. Mol Cancer Res. 2008;6:1786–93. https://doi.org/10.1158/1541-7786.MCR-08-0196.
82. Antoch MP, Toshkov I, Kuropatwinski KK, Jackson M. Deficiency in PER proteins has no effect on the rate of spontaneous and radiation-induced carcinogenesis. Cell Cycle. 2013;12:3673–80. https://doi.org/10.4161/cc.26614.
83. Mteyrek A, Filipski E, Guettier C, Okyar A, Lévi F. Clock gene Per2 as a controller of liver carcinogenesis. Oncotarget 2016;7(52):85832–85847. https://doi.org/10.18632/oncotarget.11037
84. Gu X, et al. The circadian mutation PER2(S662G) is linked to cell cycle progression and tumorigenesis. Cell Death Differ. 2012;19:397–405. https://doi.org/10.1038/cdd.2011.103.
85. Fu L, Pelicano H, Liu J, Huang P, Lee CC. The circadian gene Period2 plays an important role in tumor suppression and DNA damage response in vivo. Cell. 2002;111(1):41–50. https://doi.org/10.1016/s0092-8674(02)00961-3.
86. Peng F, et al. Oncogenic fatty acid oxidation senses circadian disruption in sleep-deficiency-enhanced tumorigenesis. Cell Metab. 2024;36:1598-1618 e1511. https://doi.org/10.1016/j.cmet.2024.04.018.
87. Janich P, et al. The circadian molecular clock creates epidermal stem cell heterogeneity. Nature. 2011;480:209–14. https://doi.org/10.1038/nature10649.
88. Brennan R, Jan JE, Lyons CJ. Light, dark, and melatonin: emerging evidence for the importance of melatonin in ocular physiology. Eye (Lond). 2007;21:901–8. https://doi.org/10.1038/sj.eye.6702597.
89. Carrillo-Vico A, Lardone PJ, Alvarez-Sanchez N, Rodriguez-Rodriguez A, Guerrero JM. Melatonin: buffering the immune system. Int J Mol Sci. 2013;14:8638–83. https://doi.org/10.3390/ijms14048638.
90. Calvo JR, Gonzalez-Yanes C, Maldonado MD. The role of melatonin in the cells of the innate immunity: a review. J Pineal Res. 2013;55:103–20. https://doi.org/10.1111/jpi.12075.
91. Cassidy RM, Lu Y, Jere M, Tian JB, Xu Y, Mangieri LR, Felix-Okoroji B, Selever J, Xu Y, Arenkiel BR, Tong Q. A lateral hypothalamus to basal forebrain neurocircuit promotes feeding by suppressing responses to anxiogenic environmental cues. Sci Adv. 2019;5(3):eaav1640. https://doi.org/10.1126/sciadv.aav1640.
92. Jennings JH, et al. Visualizing hypothalamic network dynamics for appetitive and consummatory behaviors. Cell. 2015;160:516–27. https://doi.org/10.1016/j.cell.2014.12.026.
93. Pace M. et al. Loss of Snord116 impacts lateral hypothalamus, sleep, and food-related behaviors. JCI Insight 2020;5. https://doi.org/10.1172/jci.insight.137495
94. Fakhoury M, Salman I, Najjar W, Merhej G, Lawand N. The lateral hypothalamus: an uncharted territory for processing peripheral neurogenic inflammation. Front Neurosci. 2020;14:101. https://doi.org/10.3389/fnins.2020.00101.
95. de Lecea L, Kilduff TS, Peyron C, Gao XB, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett F2, Frankel WN. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci U S A 1998;95(1):322–7.https://doi.org/10.1073/pnas.95.1.322
96. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998;92(4):573–85. https://doi.org/10.1016/s0092-8674(00)80949-6.
97. Walker WH 2nd, Borniger JC. Molecular Mechanisms of Cancer-Induced Sleep Disruption. Int J Mol Sci 2019;20. https://doi.org/10.3390/ijms20112780
98. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17:233–47. https://doi.org/10.1038/nri.2017.1.
99. Bonnavion P, Jackson AC, Carter ME, de Lecea L. Antagonistic interplay between hypocretin and leptin in the lateral hypothalamus regulates stress responses. Nat Commun. 2015;6:6266. https://doi.org/10.1038/ncomms7266.
100. Geerling JC, Mettenleiter TC, Loewy AD. Orexin neurons project to diverse sympathetic outflow systems. Neuroscience. 2003;122(2):541–50. https://doi.org/10.1016/j.neuroscience.2003.07.008.
101. Yi CX, et al. A major role for perifornical orexin neurons in the control of glucose metabolism in rats. Diabetes. 2009;58:1998–2005. https://doi.org/10.2337/db09-0385.
102. Borniger JC, et al. A Role for Hypocretin/Orexin in Metabolic and Sleep Abnormalities in a Mouse Model of Non-metastatic Breast Cancer. Cell Metab. 2018;28:118-129 e115. https://doi.org/10.1016/j.cmet.2018.04.021.
103. Verkasalo PK, et al. Sleep duration and breast cancer: a prospective cohort study. Cancer Res. 2005;65:9595–600. https://doi.org/10.1158/0008-5472.CAN-05-2138.
104. Gallicchio L, Kalesan B. Sleep duration and mortality: a systematic review and meta-analysis. J Sleep Res. 2009;18:148–58. https://doi.org/10.1111/j.1365-2869.2008.00732.x.
105. Kakizaki M, et al. Sleep duration and the risk of breast cancer: the Ohsaki Cohort Study. Br J Cancer. 2008;99:1502–5. https://doi.org/10.1038/sj.bjc.6604684.
106. McAlpine CS, et al. Sleep modulates haematopoiesis and protects against atherosclerosis. Nature. 2019;566:383–7. https://doi.org/10.1038/s41586-019-0948-2.
107. Sigurdsson T, Duvarci S. Hippocampal-prefrontal interactions in cognition, behavior and psychiatric disease. Front Syst Neurosci. 2015;9:190. https://doi.org/10.3389/fnsys.2015.00190.
108. Kalafatakis K, et al. Ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man. Proc Natl Acad Sci U S A. 2018;115:E4091–100. https://doi.org/10.1073/pnas.1714239115.
109. Cools R, Roberts AC, Robbins TW. Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci. 2008;12:31–40. https://doi.org/10.1016/j.tics.2007.10.011.
110. Strikwerda-Brown C, et al. The interplay of emotional and social conceptual processes during moral reasoning in frontotemporal dementia. Brain. 2021;144:938–52. https://doi.org/10.1093/brain/awaa435.
111. Schagen SB, et al. Monitoring and optimising cognitive function in cancer patients: Present knowledge and future directions. EJC Suppl. 2014;12:29–40. https://doi.org/10.1016/j.ejcsup.2014.03.003.
112. Fleming B, Edison P, Kenny L. Cognitive impairment after cancer treatment: mechanisms, clinical characterization, and management. BMJ. 2023;380:e071726. https://doi.org/10.1136/bmj-2022-071726.

113. Rodriguez Martin B, Fernandez Rodriguez EJ, Rihuete Galve MI, Cruz Hernandez JJ. Study of Chemotherapy-Induced Cognitive Impairment in Women with Breast Cancer. Int J Environ Res Public Health 2020;17.https://doi.org/10.3390/ijerph17238896
114. Vardy JL, et al. cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal. Controlled Study J Clin Oncol. 2015;33:4085–92. https://doi.org/10.1200/JCO.2015.63.0905.
115. Lange M, et al. cognitive impairment in patients with breast cancer before surgery: results from a CANTO cohort subgroup. Cancer Epidemiol Biomarkers Prev. 2020;29:1759–66. https://doi.org/10.1158/1055-9965.EPI-20-0346.
116. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10:34–445. https://doi.org/10.1038/nrn2639.
117. Murmu MS, et al. Changes of spine density and dendritic complexity in the prefrontal cortex in offspring of mothers exposed to stress during pregnancy. Eur J Neurosci. 2006;24:1477–87. https://doi.org/10.1111/j.1460-9568.2006.05024.x.
118. Liston C, et al. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J Neurosci. 2006;26:7870–4. https://doi.org/10.1523/JNEUROSCI.1184-06.2006.
119. Morey RA, Haswell CC, Hooper SR, De Bellis MD. Amygdala, hippocampus, and ventral medial prefrontal cortex volumes differ in maltreated youth with and without chronic posttraumatic stress disorder. Neuropsychopharmacology. 2016;41:791–801. https://doi.org/10.1038/npp.2015.205.
120. Chen Y, et al. restraint stress, foot shock and corticosterone differentially alter autophagy in the rat hippocampus, basolateral amygdala and prefrontal cortex. Neurochem Res. 2024;49:492–506. https://doi.org/10.1007/s11064-023-04048-x.
121. McEwen BS, Nasca C, Gray JD. stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacology. 2016;41:3–23. https://doi.org/10.1038/npp.2015.171.
122. Petersen J et al. GLP-1-directed NMDA receptor antagonism for obesity treatment. Nature 2024. https://doi.org/10.1038/s41586-024-07419-8
123. Hansen KB, et al. Structure, function, and pharmacology of glutamate receptor ion channels. Pharmacol Rev. 2021;73:298–487. https://doi.org/10.1124/pharmrev.120.000131.
124. Cerqueira JJ, et al. Morphological correlates of corticosteroid-induced changes in prefrontal cortex-dependent behaviors. J Neurosci. 2005;25:7792–800. https://doi.org/10.1523/JNEUROSCI.1598-05.2005.
125. Venkataramani V, et al. Glutamatergic synaptic input to glioma cells drives brain tumour progression. Nature. 2019;573:532–8. https://doi.org/10.1038/s41586-019-1564-x.
126. Stepulak A, Rola R, Polberg K, Ikonomidou C. Glutamate and its receptors in cancer. J Neural Transm (Vienna). 2014;121:933–44. https://doi.org/10.1007/s00702-014-1182-6.
127. McBrayer SK, et al. Transaminase inhibition by 2-hydroxyglutarate impairs glutamate biosynthesis and redox homeostasis in Glioma. Cell. 2018;175:101-116 e125. https://doi.org/10.1016/j.cell.2018.08.038.
128. Venkatesh HS, et al. Electrical and synaptic integration of glioma into neural circuits. Nature. 2019;573:539–45. https://doi.org/10.1038/s41586-019-1563-y.
129. Rzeski W, Turski L, Ikonomidou C. Glutamate antagonists limit tumor growth. Proc Natl Acad Sci U S A. 2001;98(11):6372–7. https://doi.org/10.1073/pnas.091113598.
130. Zeng Q, et al. Synaptic proximity enables NMDAR signalling to promote brain metastasis. Nature. 2019;573:526–31. https://doi.org/10.1038/s41586-019-1576-6.
131. Lohani S, Poplawsky AJ, Kim SG, Moghaddam B. Unexpected global impact of VTA dopamine neuron activation as measured by opto-fMRI. Mol Psychiatry. 2017;22:585–94. https://doi.org/10.1038/mp.2016.102.
132. Hamzehpour L, Bohn T, Jaspers L, Grimm O. Exploring the link between functional connectivity of ventral tegmental area and physical fitness in schizophrenia and healthy controls. Eur Neuropsychopharmacol. 2023;76:77–86. https://doi.org/10.1016/j.euroneuro.2023.07.009.
133. Morales M, Margolis EB. Ventral tegmental area: cellular heterogeneity, connectivity and behaviour. Nat Rev Neurosci. 2017;18:73–85. https://doi.org/10.1038/nrn.2016.165.
134. Kahn RS, et al. Schizophrenia. Nat Rev Dis Primers. 2015;1:15067. https://doi.org/10.1038/nrdp.2015.67.
135. Solmi M, et al. Disparities in cancer screening in people with mental illness across the world versus the general population: prevalence and comparative meta-analysis including 4 717 839 people. Lancet Psychiatry. 2020;7:52–63. https://doi.org/10.1016/S2215-0366(19)30414-6.
136. Howard LM, et al. Cancer diagnosis in people with severe mental illness: practical and ethical issues. Lancet Oncol. 2010;11:797–804. https://doi.org/10.1016/S1470-2045(10)70085-1.
137. Brown JS. Treatment of cancer with antipsychotic medications: Pushing the boundaries of schizophrenia and cancer. Neurosci Biobehav Rev. 2022;141:104809. https://doi.org/10.1016/j.neubiorev.2022.104809.
138. Khokhar JY, Henricks AM, Sullivan ED, Green AI. Unique Effects of Clozapine: A Pharmacological Perspective. Adv Pharmacol. 2018;82:137–62. https://doi.org/10.1016/bs.apha.2017.09.009.
139. Yang CE, et al. The antipsychotic chlorpromazine suppresses YAP signaling, stemness properties, and drug resistance in breast cancer cells. Chem Biol Interact. 2019;302:28–35. https://doi.org/10.1016/j.cbi.2019.01.033.
140. Fujiwara R, et al. Chlorpromazine cooperatively induces apoptosis with tyrosine kinase inhibitors in EGFR-mutated lung cancer cell lines and restores the sensitivity to gefitinib in T790M-harboring resistant cells. Biochem Biophys Res Commun. 2022;626:156–66. https://doi.org/10.1016/j.bbrc.2022.08.010.
141. Wang Q, et al. Targeting GRP75 with a Chlorpromazine Derivative Inhibits Endometrial Cancer Progression Through GRP75-IP3R-Ca(2+)-AMPK Axis. Adv Sci (Weinh). 2024;11:e2304203. https://doi.org/10.1002/advs.202304203.
142. Xu F, et al. Repurposed antipsychotic chlorpromazine inhibits colorectal cancer and pulmonary metastasis by inducing G2/M cell cycle arrest, apoptosis, and autophagy. Cancer Chemother Pharmacol. 2022;89:331–46. https://doi.org/10.1007/s00280-021-04386-z.
143. Jhou AJ, et al. Chlorpromazine, an antipsychotic agent, induces G2/M phase arrest and apoptosis via regulation of the PI3K/AKT/mTOR-mediated autophagy pathways in human oral cancer. Biochem Pharmacol. 2021;184:114403. https://doi.org/10.1016/j.bcp.2020.114403.
144. Wehrwein EA, Orer HS, Barman SM. Overview of the anatomy, physiology, and pharmacology of the autonomic nervous system. Compr Physiol. 2016;6:1239–78. https://doi.org/10.1002/cphy.c150037.
145. Carter JR, Goldstein DS. Sympathoneural and adrenomedullary responses to mental stress. Compr Physiol. 2015;5:119–46. https://doi.org/10.1002/cphy.c140030.
146. Shu LZ et al. Interactions between MDSCs and the Autonomic Nervous System: Opportunities and Challenges in Cancer Neuroscience. Cancer Immunol Res 2024;OF1-OF11.https://doi.org/10.1158/2326-6066.CIR-23-0976
147. Scott-Solomon E, Boehm E, Kuruvilla R. The sympathetic nervous system in development and disease. Nat Rev Neurosci. 2021;22:685–702. https://doi.org/10.1038/s41583-021-00523-y.
148. Ernsberger U, Rohrer H. Sympathetic tales: subdivisons of the autonomic nervous system and the impact of developmental studies. Neural Dev. 2018;13:20. https://doi.org/10.1186/s13064-018-0117-6.
149. Zheng S, et al. Extracellular vesicle-packaged PIAT from cancer-associated fibroblasts drives neural remodeling by mediating m5C modification in pancreatic cancer mouse models. Sci Transl Med. 2024;16:eadi0178. https://doi.org/10.1126/scitranslmed.adi0178.
150. Padmanaban V, et al. Neuronal substance P drives metastasis through an extracellular RNA-TLR7 axis. Nature. 2024;633:207–15. https://doi.org/10.1038/s41586-024-07767-5.
151. Simo M, Navarro X, Yuste VJ, Bruna J. Autonomic nervous system and cancer. Clin Auton Res. 2018;28:301–14. https://doi.org/10.1007/s10286-018-0523-1.
152. Kamiya A, Hiyama T, Fujimura A, Yoshikawa S. Sympathetic and parasympathetic innervation in cancer: therapeutic implications. Clin Auton Res. 2021;31:165–78. https://doi.org/10.1007/s10286-020-00724-y.
153. Eichmann A, Thomas JL. Molecular parallels between neural and vascular development. Cold Spring Harb Perspect Med. 2013;3:a006551. https://doi.org/10.1101/cshperspect.a006551.
154. Dobrenis K, Gauthier LR, Barroca V, Magnon C. Granulocyte colony-stimulating factor off-target effect on nerve outgrowth promotes prostate

cancer development. Int J Cancer. 2015;136:982–8. https://doi.org/10.1002/ijc.29046.
155. Magnon C, et al. Autonomic nerve development contributes to prostate cancer progression. Science. 2013;341:1236361. https://doi.org/10.1126/science.1236361.
156. Mauffrey P, et al. Progenitors from the central nervous system drive neurogenesis in cancer. Nature. 2019;569:672–8. https://doi.org/10.1038/s41586-019-1219-y.
157. Ding Y, et al. Semaphorin 4F as a critical regulator of neuroepithelial interactions and a biomarker of aggressive prostate cancer. Clin Cancer Res. 2013;19:6101–11. https://doi.org/10.1158/1078-0432.CCR-12-3669.
158. Ayala GE, et al. Cancer-related axonogenesis and neurogenesis in prostate cancer. Clin Cancer Res. 2008;14:7593–603. https://doi.org/10.1158/1078-0432.CCR-08-1164.
159. Findlay Q, Yap KK, Bergner AJ, Young HM, Stamp LA. Enteric neural progenitors are more efficient than brain-derived progenitors at generating neurons in the colon. Am J Physiol Gastrointest Liver Physiol. 2014;307:G741-748. https://doi.org/10.1152/ajpgi.00225.2014.
160. Zarco N, Norton E, Quinones-Hinojosa A, Guerrero-Cazares H. Overlapping migratory mechanisms between neural progenitor cells and brain tumor stem cells. Cell Mol Life Sci. 2019;76:3553–70. https://doi.org/10.1007/s00018-019-03149-7.
161. Wu Y, Zhou L, Zhang X, Yang X, Niedermann G, Xue J. Psychological distress and eustress in cancer and cancer treatment: Advances and perspectives. Sci Adv. 2022;8(47):eabq7982. https://doi.org/10.1126/sciadv.abq7982.
162. Xia Y, et al. Catecholamines contribute to the neovascularization of lung cancer via tumor-associated macrophages. Brain Behav Immun. 2019;81:111–21. https://doi.org/10.1016/j.bbi.2019.06.004.
163. Kim-Fuchs C, et al. Chronic stress accelerates pancreatic cancer growth and invasion: a critical role for beta-adrenergic signaling in the pancreatic microenvironment. Brain Behav Immun. 2014;40:40–7. https://doi.org/10.1016/j.bbi.2014.02.019.
164. Demir IE, Friess H, Ceyhan GO. Nerve-cancer interactions in the stromal biology of pancreatic cancer. Front Physiol. 2012;3:97. https://doi.org/10.3389/fphys.2012.00097.
165. Apte MV, Wilson JS, Lugea A, Pandol SJ. A starring role for stellate cells in the pancreatic cancer microenvironment. Gastroenterology. 2013;144:1210–9. https://doi.org/10.1053/j.gastro.2012.11.037.
166. Guillot J, et al. Sympathetic axonal sprouting induces changes in macrophage populations and protects against pancreatic cancer. Nat Commun. 2024;13:1985. https://doi.org/10.1038/s41467-022-29659-w.
167. Lamkin DM, Sloan EK, Patel AJ, Chiang BS, Pimentel MA, Ma JC, Arevalo JM, Morizono K, Cole SW. Chronic stress enhances progression of acute lymphoblastic leukemia via β-adrenergic signaling. Brain Behav Immun. 2012;26(4):635–41. https://doi.org/10.1016/j.bbi.2012.01.013.
168. Liu Y, Yu X, Zhuang J. Epinephrine stimulates cell proliferation and induces chemoresistance in myeloma cells through the beta-adrenoreceptor in vitro. Acta Haematol. 2017;138:103–10. https://doi.org/10.1159/000478517.
169. Wu FQ, et al. ADRB2 signaling promotes HCC progression and sorafenib resistance by inhibiting autophagic degradation of HIF1alpha. J Hepatol. 2016;65:314–24. https://doi.org/10.1016/j.jhep.2016.04.019.
170. Zahalka AH, Arnal-Estapé A, Maryanovich M, Nakahara F, Cruz CD, Finley LW, Frenette PS. Adrenergic nerves activate an angio-metabolic switch in prostate cancer. Science. 2017;358(6361):321–6. https://doi.org/10.1126/science.aah5072.
171. Conceicao F, Sousa DM, Paredes J, Lamghari M. Sympathetic activity in breast cancer and metastasis: partners in crime. Bone Res. 2021;9:9. https://doi.org/10.1038/s41413-021-00137-1.
172. Zhang L, Guo L, Tao M, Fu W, Xiu D. Parasympathetic neurogenesis is strongly associated with tumor budding and correlates with an adverse prognosis in pancreatic ductal adenocarcinoma. Chin J Cancer Res 2016;28:180–186.https://doi.org/10.21147/j.issn.1000-9604.2016.02.05
173. Song P, et al. M3 muscarinic receptor antagonists inhibit small cell lung carcinoma growth and mitogen-activated protein kinase phosphorylation induced by acetylcholine secretion. Cancer Res. 2007;67:3936–44. https://doi.org/10.1158/0008-5472.CAN-06-2484.
174. Konishi M, Hayakawa Y, Koike K. Role of muscarinic acetylcholine signaling in gastrointestinal cancers. Biomedicines 2019;7. https://doi.org/10.3390/biomedicines7030058
175. Belo A, et al. Muscarinic receptor agonists stimulate human colon cancer cell migration and invasion. Am J Physiol Gastrointest Liver Physiol. 2011;300:G749-760. https://doi.org/10.1152/ajpgi.00306.2010.
176. Kodaira M, et al. Functional muscarinic m3 receptor expressed in gastric cancer cells stimulates tyrosine phosphorylation and MAP kinase. J Gastroenterol. 1999;34:163–71. https://doi.org/10.1007/s005350050238.
177. Zhang L, et al. High expression of muscarinic acetylcholine receptor 3 predicts poor prognosis in patients with pancreatic ductal adenocarcinoma. Onco Targets Ther. 2016;9:6719–26. https://doi.org/10.2147/OTT.S111382.
178. Zhang L, et al. Sympathetic and parasympathetic innervation in hepatocellular carcinoma. Neoplasma. 2017;64:840–6. https://doi.org/10.4149/neo_2017_605.
179. Partecke LI et al. Subdiaphragmatic vagotomy promotes tumor growth and reduces survival via TNFalpha in a murine pancreatic cancer model. Oncotarget 2017;8:22501–22512. https://doi.org/10.18632/oncotarget.15019
180. Dubeykovskaya Z, et al. Neural innervation stimulates splenic TFF2 to arrest myeloid cell expansion and cancer. Nat Commun. 2016;7:10517. https://doi.org/10.1038/ncomms10517.
181. Medjber K, et al. Role of nicotinic acetylcholine receptors in cell proliferation and tumour invasion in broncho-pulmonary carcinomas. Lung Cancer. 2015;87:258–64. https://doi.org/10.1016/j.lungcan.2015.01.001.
182. Harwood DSL, et al. Glioblastoma cells increase expression of notch signaling and synaptic genes within infiltrated brain tissue. Nat Commun. 2024;15:7857. https://doi.org/10.1038/s41467-024-52167-y.
183. Monje M. Synaptic communication in brain cancer. Cancer Res. 2020;80:2979–82. https://doi.org/10.1158/0008-5472.CAN-20-0646.
184. Venkataramani V, Tanev DI, Kuner T, Wick W, Winkler F. Synaptic input to brain tumors: clinical implications. Neuro Oncol. 2021;23:23–33. https://doi.org/10.1093/neuonc/noaa158.
185. Allen NJ. Brain tumours manipulate neighbouring synapses. Nature. 2020;578:46–7. https://doi.org/10.1038/d41586-020-00137-x.
186. Rosas-Ballina M, et al. Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia. Proc Natl Acad Sci U S A. 2008;105:11008–13. https://doi.org/10.1073/pnas.0803237105.
187. Madden KS, Felten DL. Experimental basis for neural-immune interactions. Physiol Rev. 1995;75:77–106. https://doi.org/10.1152/physrev.1995.75.1.77.
188. Dantzer R. Neuroimmune interactions: from the brain to the immune system and vice versa. Physiol Rev. 2018;98:477–504. https://doi.org/10.1152/physrev.00039.2016.
189. Lewitus GM, Pribiag H, Duseja R, St-Hilaire M, Stellwagen D. An adaptive role of TNFalpha in the regulation of striatal synapses. J Neurosci. 2014;34:6146–55. https://doi.org/10.1523/JNEUROSCI.3481-13.2014.
190. Santello M, Volterra A. TNFalpha in synaptic function: switching gears. Trends Neurosci. 2012;35:638–47. https://doi.org/10.1016/j.tins.2012.06.001.
191. Barria A. Dangerous liaisons as tumour cells form synapses with neurons. Nature. 2019;573:499–501. https://doi.org/10.1038/d41586-019-02746-7.
192. Turk AZ, Marchoubeh ML, Fritsch I, Maguire GA, SheikhBahaei S. Dopamine, vocalization, and astrocytes. Brain Lang. 2021;219:104970. https://doi.org/10.1016/j.bandl.2021.104970.
193. Eisenhofer G, et al. Substantial production of dopamine in the human gastrointestinal tract. J Clin Endocrinol Metab. 1997;82:3864–71. https://doi.org/10.1210/jcem.82.11.4339.
194. Zhang X, Liu Q, Liao Q, Zhao Y. potential roles of peripheral dopamine in tumor immunity. J Cancer. 2017;8:2966–73. https://doi.org/10.7150/jca.20850.
195. Jenkins PO, Mehta MA, Sharp DJ. Catecholamines and cognition after traumatic brain injury. Brain. 2016;139:2345–71. https://doi.org/10.1093/brain/aww128.
196. Marazziti D, Poletti M, Dell'Osso L, Baroni S, Bonuccelli U. Prefrontal cortex, dopamine, and jealousy endophenotype. CNS Spectr. 2013;18:6–14. https://doi.org/10.1017/S1092852912000740.
197. Baik JH. Dopamine signaling in reward-related behaviors. Front Neural Circuits. 2013;7:152. https://doi.org/10.3389/fncir.2013.00152.
198. Wu M, et al. Dopamine pathways mediating affective state transitions after sleep loss. Neuron. 2024;112:141-154 e148. https://doi.org/10.1016/j.neuron.2023.10.002.

199. Vousooghi N, Zarei SZ, Sadat-Shirazi MS, Eghbali F, Zarrindast MR. mRNA expression of dopamine receptors in peripheral blood lymphocytes of computer game addicts. J Neural Transm (Vienna). 2015;122:1391–8. https://doi.org/10.1007/s00702-015-1408-2.
200. Nutt DJ, Lingford-Hughes A, Erritzoe D, Stokes PR. The dopamine theory of addiction: 40 years of highs and lows. Nat Rev Neurosci. 2015;16:305–12. https://doi.org/10.1038/nrn3939.
201. Saha B, Mondal AC, Basu S, Dasgupta PS. Circulating dopamine level, in lung carcinoma patients, inhibits proliferation and cytotoxicity of CD4+ and CD8+ T cells by D1 dopamine receptors: an in vitro analysis. Int Immunopharmacol. 2001;1:1363–74. https://doi.org/10.1016/s1567-5769(01)00068-6.
202. Gao J, Zhang C, Gao F, Li H. The effect and mechanism of dopamine D1 receptors on the proliferation of osteosarcoma cells. Mol Cell Biochem. 2017;430:31–6. https://doi.org/10.1007/s11010-017-2951-y.
203. Xue Z, et al. The dopamine receptor D1 inhibitor, SKF83566, suppresses GBM stemness and invasion through the DRD1-c-Myc-UHRF1 interactions. J Exp Clin Cancer Res. 2024;43:25. https://doi.org/10.1186/s13046-024-02947-7.
204. Lu X, et al. Research progress on the roles of dopamine and dopamine receptors in digestive system diseases. J Cell Mol Med. 2024;28:e18154. https://doi.org/10.1111/jcmm.18154.
205. Bakhtou H, Olfatbakhsh A, Deezagi A, Ahangari G. The Expression of Dopamine Receptors Gene and their Potential Role in Targeting Breast Cancer Cells with Selective Agonist and Antagonist Drugs. Could it be the Novel Insight to Therapy? Curr Drug Discov Technol 2019;16:184–197.https://doi.org/10.2174/1570163815666180130101421
206. Mu J, et al. Dopamine receptor D2 is correlated with gastric cancer prognosis. Oncol Lett. 2017;13:1223–7. https://doi.org/10.3892/ol.2017.5573.
207. Mao M, Yu T, Hu J, Hu L. Dopamine D2 receptor blocker thioridazine induces cell death in human uterine cervical carcinoma cell line SiHa. J Obstet Gynaecol Res. 2015;41:1240–5. https://doi.org/10.1111/jog.12691.
208. Hoeppner LH, et al. Dopamine D2 receptor agonists inhibit lung cancer progression by reducing angiogenesis and tumor infiltrating myeloid derived suppressor cells. Mol Oncol. 2015;9:270–81. https://doi.org/10.1016/j.molonc.2014.08.008.
209. Huang H, et al. Dopamine D2 receptor suppresses gastric cancer cell invasion and migration via inhibition of EGFR/AKT/MMP-13 pathway. Int Immunopharmacol. 2016;39:113–20. https://doi.org/10.1016/j.intimp.2016.07.002.
210. Tan Y, et al. Tumor suppressor DRD2 facilitates M1 macrophages and restricts NF-kappaB signaling to trigger pyroptosis in breast cancer. Theranostics. 2021;11:5214–31. https://doi.org/10.7150/thno.58322.
211. Owen DH, Trikalinos NA. Neuroendocrine and Rare Tumor Advances: A New and Promising TRAIL Emerges. Clin Cancer Res. 2022;28:1748–50. https://doi.org/10.1158/1078-0432.CCR-22-0120.
212. Shaw V, Srivastava S, Srivastava SK. Repurposing antipsychotics of the diphenylbutylpiperidine class for cancer therapy. Semin Cancer Biol. 2021;68:75–83. https://doi.org/10.1016/j.semcancer.2019.10.007.
213. Yang Y, et al. Repositioning Dopamine D2 Receptor Agonist Bromocriptine to Enhance Docetaxel Chemotherapy and Treat Bone Metastatic Prostate Cancer. Mol Cancer Ther. 2018;17:1859–70. https://doi.org/10.1158/1535-7163.MCT-17-1176.
214. Li J, et al. Dopamine D2 receptor antagonist sulpiride enhances dexamethasone responses in the treatment of drug-resistant and metastatic breast cancer. Acta Pharmacol Sin. 2017;38:1282–96. https://doi.org/10.1038/aps.2017.24.
215. Shi L, et al. The DRD2 Antagonist Haloperidol Mediates Autophagy-Induced Ferroptosis to Increase Temozolomide Sensitivity by Promoting Endoplasmic Reticulum Stress in Glioblastoma. Clin Cancer Res. 2023;29:3172–88. https://doi.org/10.1158/1078-0432.CCR-22-3971.
216. Weissenrieder JS, et al. The Dopamine D2 Receptor Contributes to the Spheroid Formation Behavior of U87 Glioblastoma Cells. Pharmacology. 2020;105:19–27. https://doi.org/10.1159/000502562.
217. Dai WL, et al. Blockade of spinal dopamine D1/D2 receptor suppresses activation of NMDA receptor through Galphaq and Src kinase to attenuate chronic bone cancer pain. J Adv Res. 2021;28:139–48. https://doi.org/10.1016/j.jare.2020.08.005.
218. Iovino L, Tremblay ME, Civiero L. Glutamate-induced excitotoxicity in Parkinson's disease: The role of glial cells. J Pharmacol Sci. 2020;144:151–64. https://doi.org/10.1016/j.jphs.2020.07.011.
219. Zhou Y, Danbolt NC. Glutamate as a neurotransmitter in the healthy brain. J Neural Transm (Vienna). 2014;121:799–817. https://doi.org/10.1007/s00702-014-1180-8.
220. Zhang D, Hua Z, Li Z. The role of glutamate and glutamine metabolism and related transporters in nerve cells. CNS Neurosci Ther. 2024;30:e14617. https://doi.org/10.1111/cns.14617.
221. Pereira MS, Klamt F, Thomé CC, Worm PV, de Oliveira DL. Metabotropic glutamate receptors as a new therapeutic target for malignant gliomas. Oncotarget 2017;8:22279–22298.https://doi.org/10.18632/oncotarget.15299
222. Willard SS, Koochekpour S. Glutamate signaling in benign and malignant disorders: current status, future perspectives, and therapeutic implications. Int J Biol Sci. 2013;9:728–42. https://doi.org/10.7150/ijbs.6475.
223. Warlow SM, et al. Mesoaccumbal glutamate neurons drive reward via glutamate release but aversion via dopamine co-release. Neuron. 2024;112:488-499 e485. https://doi.org/10.1016/j.neuron.2023.11.002.
224. Ye ZC, Sontheimer H. Glioma cells release excitotoxic concentrations of glutamate. Cancer Res. 1999;59:4383–91.
225. Prickett TD, Samuels Y. Molecular pathways: dysregulated glutamatergic signaling pathways in cancer. Clin Cancer Res. 2012;18:4240–6. https://doi.org/10.1158/1078-0432.CCR-11-1217.
226. Teh JL, Chen S. Glutamatergic signaling in cellular transformation. Pigment Cell Melanoma Res. 2012;25:331–42. https://doi.org/10.1111/j.1755-148X.2012.00983.x.
227. Kalariti N, Pissimissis N, Koutsilieris M. The glutamatergic system outside the CNS and in cancer biology. Expert Opin Investig Drugs. 2005;14:1487–96. https://doi.org/10.1517/13543784.14.12.1487.
228. Cavalheiro EA, Olney JW. Glutamate antagonists: deadly liaisons with cancer. Proc Natl Acad Sci U S A. 2001;98:5947–8. https://doi.org/10.1073/pnas.121179198.
229. Xie L, et al. A (211)At-labelled mGluR1 inhibitor induces cancer senescence to elicit long-lasting anti-tumor efficacy. Cell Rep Med. 2023;4:100960. https://doi.org/10.1016/j.xcrm.2023.100960.
230. Gomez V, et al. HER2 Mediates PSMA/mGluR1-Driven Resistance to the DS-7423 Dual PI3K/mTOR Inhibitor in PTEN Wild-type Prostate Cancer Models. Mol Cancer Ther. 2022;21:667–76. https://doi.org/10.1158/1535-7163.MCT-21-0320.
231. Ishibashi K, et al. Astrocyte-induced mGluR1 activates human lung cancer brain metastasis via glutamate-dependent stabilization of EGFR. Dev Cell. 2024;59:579-594 e576. https://doi.org/10.1016/j.devcel.2024.01.010.
232. Yang C, et al. SIRT1 Activation Attenuates Bone Cancer Pain by Inhibiting mGluR1/5. Cell Mol Neurobiol. 2019;39:1165–75. https://doi.org/10.1007/s10571-019-00710-7.
233. Zhou CH, et al. SIRT1 attenuates neuropathic pain by epigenetic regulation of mGluR1/5 expressions in type 2 diabetic rats. Pain. 2017;158:130–9. https://doi.org/10.1097/j.pain.0000000000000739.
234. Wen Y, et al. Activation of the glutamate receptor GRM1 enhances angiogenic signaling to drive melanoma progression. Cancer Res. 2014;74:2499–509. https://doi.org/10.1158/0008-5472.CAN-13-1531.
235. Mehnert JM, et al. A phase II trial of riluzole, an antagonist of metabotropic glutamate receptor 1 (GRM1) signaling, in patients with advanced melanoma. Pigment Cell Melanoma Res. 2018;31:534–40. https://doi.org/10.1111/pcmr.12694.
236. Deutsch SI, Tang AH, Burket JA, Benson AD. NMDA receptors on the surface of cancer cells: target for chemotherapy? Biomed Pharmacother. 2014;68:493–6. https://doi.org/10.1016/j.biopha.2014.03.012.
237. Stepulak A, et al. Expression of glutamate receptor subunits in human cancers. Histochem Cell Biol. 2009;132:435–45. https://doi.org/10.1007/s00418-009-0613-1.
238. Liu JW, et al. Quantitative hypermethylation of NMDAR2B in human gastric cancer. Int J Cancer. 2007;121:1994–2000. https://doi.org/10.1002/ijc.22934.
239. Kim MS, et al. N-methyl-D-aspartate receptor type 2B is epigenetically inactivated and exhibits tumor-suppressive activity in human esophageal cancer. Cancer Res. 2006;66:3409–18. https://doi.org/10.1158/0008-5472.CAN-05-1608.

240. Tamura H, et al. Aberrant methylation of N-methyl-D-aspartate receptor type 2B (NMDAR2B) in non-small cell carcinoma. BMC Cancer. 2011;11:220. https://doi.org/10.1186/1471-2407-11-220.
241. Li L, Hanahan D. Hijacking the neuronal NMDAR signaling circuit to promote tumor growth and invasion. Cell. 2013;153:86–100. https://doi.org/10.1016/j.cell.2013.02.051.
242. Dore K, et al. Unconventional NMDA Receptor Signaling. J Neurosci. 2017;37:10800–7. https://doi.org/10.1523/JNEUROSCI.1825-17.2017.
243. Xu F, et al. A Combinatorial CRISPR-Cas9 Screen Identifies Ifenprodil as an Adjunct to Sorafenib for Liver Cancer Treatment. Cancer Res. 2021;81:6219–32. https://doi.org/10.1158/0008-5472.CAN-21-1017.
244. Lutz H, Nguyen TA, Joswig J, Rau K, Laube B. NMDA Receptor Signaling Mediates cFos Expression via Top2beta-Induced DSBs in Glioblastoma Cells. Cancers (Basel) 2019;11. https://doi.org/10.3390/cancers11030306
245. Haffner MC, et al. Androgen-induced TOP2B-mediated double-strand breaks and prostate cancer gene rearrangements. Nat Genet. 2010;42:668–75. https://doi.org/10.1038/ng.613.
246. Madabhushi R, et al. Activity-induced DNA breaks govern the expression of neuronal early-response genes. Cell. 2015;161:1592–605. https://doi.org/10.1016/j.cell.2015.05.032.
247. Li F, et al. Glutamate from nerve cells promotes perineural invasion in pancreatic cancer by regulating tumor glycolysis through HK2 mRNA-m6A modification. Pharmacol Res. 2023;187:106555. https://doi.org/10.1016/j.phrs.2022.106555.
248. Chen J, et al. Reprogramming immunosuppressive myeloid cells by activated T cells promotes the response to anti-PD-1 therapy in colorectal cancer. Signal Transduct Target Ther. 2021;6:4. https://doi.org/10.1038/s41392-020-00377-3.
249. Haddad YW, Korcari E, Polsinelli GN, Yuchuan D. The effect of cocaine and methamphetamine on saccular aneurysm formation and rupture: A literature review. Brain Hemorrhages. 2021;2:111–5. https://doi.org/10.1016/j.hest.2020.11.002.
250. Kannen V, Bader M, Sakita JY, Uyemura SA, Squire JA. The dual role of serotonin in colorectal cancer. Trends Endocrinol Metab. 2020;31:611–25. https://doi.org/10.1016/j.tem.2020.04.008.
251. Rozenblit-Susan S, Chapnik N, Froy O. Serotonin prevents differentiation of brown adipocytes by interfering with their clock. Obesity (Silver Spring). 2019;27:2018–24. https://doi.org/10.1002/oby.22606.
252. Karmakar S, Lal G. Role of serotonin receptor signaling in cancer cells and anti-tumor immunity. Theranostics. 2021;11:5296–312. https://doi.org/10.7150/thno.55986.
253. Lund ML, et al. L-cell differentiation is induced by bile acids through GPBAR1 and paracrine GLP-1 and serotonin signaling. Diabetes. 2020;69:614–23. https://doi.org/10.2337/db19-0764.
254. Salaciak K, Pytka K. Biased agonism in drug discovery: Is there a future for biased 5-HT(1A) receptor agonists in the treatment of neuropsychiatric diseases? Pharmacol Ther. 2021;227:107872. https://doi.org/10.1016/j.pharmthera.2021.107872.
255. Song NN, et al. Enhanced dendritic morphogenesis of adult hippocampal newborn neurons in central 5-HT-deficient mice. Stem Cell Res. 2017;19:6–11. https://doi.org/10.1016/j.scr.2016.12.018.
256. Ye D, et al. The role of 5-HT metabolism in cancer. Biochim Biophys Acta Rev Cancer. 2021;1876:188618. https://doi.org/10.1016/j.bbcan.2021.188618.
257. Ruddell RG, Mann DA, Ramm GA. The function of serotonin within the liver. J Hepatol. 2008;48:666–75. https://doi.org/10.1016/j.jhep.2008.01.006.
258. Lesurtel M, Soll C, Humar B, Clavien PA. Serotonin: a double-edged sword for the liver? Surgeon. 2012;10:107–13. https://doi.org/10.1016/j.surge.2011.11.002.
259. Shu B, et al. Serotonin and YAP/VGLL4 balance correlated with progression and poor prognosis of hepatocellular carcinoma. Sci Rep. 2018;8:9739. https://doi.org/10.1038/s41598-018-28075-9.
260. Soll C, et al. Expression of serotonin receptors in human hepatocellular cancer. Clin Cancer Res. 2012;18:5902–10. https://doi.org/10.1158/1078-0432.CCR-11-1813.
261. Niture S, et al. Serotonin induced hepatic steatosis is associated with modulation of autophagy and notch signaling pathway. Cell Commun Signal. 2018;16:78. https://doi.org/10.1186/s12964-018-0282-6.
262. Dizeyi N, et al. Expression of serotonin receptors and role of serotonin in human prostate cancer tissue and cell lines. Prostate. 2004;59:328–36. https://doi.org/10.1002/pros.10374.
263. Dizeyi N, et al. Expression of serotonin receptors 2B and 4 in human prostate cancer tissue and effects of their antagonists on prostate cancer cell lines. Eur Urol. 2005;47:895–900. https://doi.org/10.1016/j.eururo.2005.02.006.
264. Gautam J, et al. Tryptophan hydroxylase 1 and 5-HT(7) receptor preferentially expressed in triple-negative breast cancer promote cancer progression through autocrine serotonin signaling. Mol Cancer. 2016;15:75. https://doi.org/10.1186/s12943-016-0559-6.
265. Nocito A, et al. Serotonin regulates macrophage-mediated angiogenesis in a mouse model of colon cancer allografts. Cancer Res. 2008;68:5152–8. https://doi.org/10.1158/0008-5472.CAN-08-0202.
266. Zhu P, et al. 5-hydroxytryptamine produced by enteric serotonergic neurons initiates colorectal cancer stem cell self-renewal and tumorigenesis. Neuron. 2022;110:2268-2282 e2264. https://doi.org/10.1016/j.neuron.2022.04.024.
267. Jiang SH, et al. Increased serotonin signaling contributes to the warburg effect in pancreatic tumor cells under metabolic stress and promotes growth of pancreatic tumors in mice. Gastroenterology. 2017;153:277-291 e219. https://doi.org/10.1053/j.gastro.2017.03.008.
268. Tu RH, et al. Neurotransmitter Receptor HTR2B Regulates Lipid Metabolism to Inhibit Ferroptosis in Gastric Cancer. Cancer Res. 2023;83:3868–85. https://doi.org/10.1158/0008-5472.CAN-23-1012.
269. Christensen DK et al. SSRI use and clinical outcomes in epithelial ovarian cancer. Oncotarget 2016;7:33179–33191.https://doi.org/10.18632/oncotarget.8891
270. Liu Y, Zhang H, Wang Z, Wu P, Gong W. 5-Hydroxytryptamine1a receptors on tumour cells induce immune evasion in lung adenocarcinoma patients with depression via autophagy/pSTAT3. Eur J Cancer. 2019;114:8–24. https://doi.org/10.1016/j.ejca.2019.03.017.
271. Tu Y, et al. 5-Hydroxytryptamine activates a 5-HT/c-Myc/SLC6A4 signaling loop in non-small cell lung cancer. Biochim Biophys Acta Gen Subj. 2022;1866:130093. https://doi.org/10.1016/j.bbagen.2022.130093.
272. Wang X, et al. A GAPDH serotonylation system couples CD8(+) T cell glycolytic metabolism to antitumor immunity. Mol Cell. 2024;84:760-775 e767. https://doi.org/10.1016/j.molcel.2023.12.015.
273. Hellstrand K, Hermodsson S. Role of serotonin in the regulation of human natural killer cell cytotoxicity. J Immunol. 1987;139:869–75.
274. Iken K, Chheng S, Fargin A, Goulet AC, Kouassi E. Serotonin upregulates mitogen-stimulated B lymphocyte proliferation through 5-HT1A receptors. Cell Immunol. 1995;163:1–9. https://doi.org/10.1006/cimm.1995.1092.
275. Koh W, Kwak H, Cheong E, Lee CJ. GABA tone regulation and its cognitive functions in the brain. Nat Rev Neurosci. 2023;24:523–39. https://doi.org/10.1038/s41583-023-00724-7.
276. Huang D, et al. Cancer-cell-derived GABA promotes beta-catenin-mediated tumour growth and immunosuppression. Nat Cell Biol. 2022;24:230–41. https://doi.org/10.1038/s41556-021-00820-9.
277. Huang D, Alexander PB, Li QJ, Wang XF. GABAergic signaling beyond synapses: an emerging target for cancer therapy. Trends Cell Biol. 2023;33:403–12. https://doi.org/10.1016/j.tcb.2022.08.004.
278. Qian X, et al. Current status of GABA receptor subtypes in analgesia. Biomed Pharmacother. 2023;168:115800. https://doi.org/10.1016/j.biopha.2023.115800.
279. Jiang S-H, et al. GABRP regulates chemokine signalling, macrophage recruitment and tumour progression in pancreatic cancer through tuning KCNN4-mediated Ca2+ signalling in a GABA-independent manner. Gut. 2019;68:1994–2006. https://doi.org/10.1136/gutjnl-2018-317479.
280. Tagore M, et al. GABA Regulates Electrical Activity and Tumor Initiation in Melanoma. Cancer Discov. 2023;13:2270–91. https://doi.org/10.1158/2159-8290.CD-23-0389.
281. Bao H, et al. GABA induced by sleep deprivation promotes the proliferation and migration of colon tumors through miR-223–3p endogenous pathway and exosome pathway. J Exp Clin Cancer Res. 2023;42:344. https://doi.org/10.1186/s13046-023-02921-9.
282. Huang W, Cao L. Targeting GABA signalling for cancer treatment. Nat Cell Biol. 2022;24:131–2. https://doi.org/10.1038/s41556-021-00839-y.

283. Nair PC, McKinnon RA, Miners JO, Bastiampillai T. Binding of clozapine to the GABA(B) receptor: clinical and structural insights. Mol Psychiatry. 2020;25:1910–9. https://doi.org/10.1038/s41380-020-0709-5.
284. Evenseth LS, Gabrielsen M, Sylte I. The GABA(B) Receptor-Structure, Ligand Binding and Drug Development. Molecules 2020;25. https://doi.org/10.3390/molecules25133093
285. Tu H, et al. Dominant role of GABAB2 and Gbetagamma for GABAB receptor-mediated-ERK1/2/CREB pathway in cerebellar neurons. Cell Signal. 2007;19:1996–2002. https://doi.org/10.1016/j.cellsig.2007.05.004.
286. Kanbara K, et al. GABA(B) receptor regulates proliferation in the high-grade chondrosarcoma cell line OUMS-27 via apoptotic pathways. BMC Cancer. 2018;18:263. https://doi.org/10.1186/s12885-018-4149-4.
287. Zhang B, et al. B cell-derived GABA elicits IL-10(+) macrophages to limit anti-tumour immunity. Nature. 2021;599:471–6. https://doi.org/10.1038/s41586-021-04082-1.
288. Tessarollo L. Pleiotropic functions of neurotrophins in development. Cytokine Growth Factor Rev. 1998;9:125–37. https://doi.org/10.1016/s1359-6101(98)00003-3.
289. Rahman MM, et al. Exploring the Therapeutic Effect of Neurotrophins and Neuropeptides in Neurodegenerative Diseases: at a Glance. Mol Neurobiol. 2023;60:4206–31. https://doi.org/10.1007/s12035-023-03328-5.
290. Sasahira T, et al. Trks are novel oncogenes involved in the induction of neovascularization, tumor progression, and nodal metastasis in oral squamous cell carcinoma. Clin Exp Metastasis. 2013;30:165–76. https://doi.org/10.1007/s10585-012-9525-x.
291. Thiele CJ, Li Z, McKee AE. On Trk–the TrkB signal transduction pathway is an increasingly important target in cancer biology. Clin Cancer Res. 2009;15:5962–7. https://doi.org/10.1158/1078-0432.CCR-08-0651.
292. Garrido MP, Torres I, Vega M, Romero C. Angiogenesis in Gynecological Cancers: Role of Neurotrophins. Front Oncol. 2019;9:913. https://doi.org/10.3389/fonc.2019.00913.
293. Yu X, Liu L, Cai B, He Y, Wan X. Suppression of anoikis by the neurotrophic receptor TrkB in human ovarian cancer. Cancer Sci. 2008;99:543–52. https://doi.org/10.1111/j.1349-7006.2007.00722.x.
294. Bouzas-Rodriguez J, et al. Neurotrophin-3 production promotes human neuroblastoma cell survival by inhibiting TrkC-induced apoptosis. J Clin Invest. 2010;120:850–8. https://doi.org/10.1172/JCI41013.
295. Yin T, et al. Breaking NGF-TrkA immunosuppression in melanoma sensitizes immunotherapy for durable memory T cell protection. Nat Immunol. 2024;25:268–81. https://doi.org/10.1038/s41590-023-01723-7.
296. Zhang Y, et al. FBXO22 mediates the NGF/TRKA signaling pathway in bone metastases in prostate cancer. Am J Pathol. 2023;193:1248–66. https://doi.org/10.1016/j.ajpath.2023.05.012.
297. Tani T, Oikawa M, Misaka T, Ishida T, Takeishi Y. Heart Failure Post-Myocardial Infarction Promotes Mammary Tumor Growth Through the NGF-TRKA Pathway. JACC CardioOncol. 2024;6:55–66. https://doi.org/10.1016/j.jaccao.2023.10.002.
298. Kobayashi H et al. Neuro-mesenchymal interaction mediated by a beta2 adrenergic-nerve growth factor feedforward loop promotes colorectal cancer progression. Cancer Discov 2024. https://doi.org/10.1158/2159-8290.CD-24-0287
299. Au CW, et al. Tyrosine kinase B receptor and BDNF expression in ovarian cancers - Effect on cell migration, angiogenesis and clinical outcome. Cancer Lett. 2009;281:151–61. https://doi.org/10.1016/j.canlet.2009.02.025.
300. Lam CT, et al. Brain-derived neurotrophic factor promotes tumorigenesis via induction of neovascularization: implication in hepatocellular carcinoma. Clin Cancer Res. 2011;17:3123–33. https://doi.org/10.1158/1078-0432.CCR-10-2802.
301. Jin Z, et al. The cross-talk between tumor cells and activated fibroblasts mediated by lactate/BDNF/TrkB signaling promotes acquired resistance to anlotinib in human gastric cancer. Redox Biol. 2021;46:102076. https://doi.org/10.1016/j.redox.2021.102076.
302. Cao L, et al. Environmental and genetic activation of a brain-adipocyte BDNF/leptin axis causes cancer remission and inhibition. Cell. 2010;142:52–64. https://doi.org/10.1016/j.cell.2010.05.029.
303. Baral P, Udit S, Chiu IM. Pain and immunity: implications for host defence. Nat Rev Immunol. 2019;19:433–47. https://doi.org/10.1038/s41577-019-0147-2.
304. Foster SL, Seehus CR, Woolf CJ, Talbot S. Sense and immunity: context-dependent neuro-immune interplay. Front Immunol. 2017;8:1463. https://doi.org/10.3389/fimmu.2017.01463.
305. Mashaghi A, et al. Neuropeptide substance P and the immune response. Cell Mol Life Sci. 2016;73:4249–64. https://doi.org/10.1007/s00018-016-2293-z.
306. Holzmann B. Antiinflammatory activities of CGRP modulating innate immune responses in health and disease. Curr Protein Pept Sci. 2013;14:268–74. https://doi.org/10.2174/13892037113149990046.
307. Tsuru S, et al. RAMP1 signaling in immune cells regulates inflammation-associated lymphangiogenesis. Lab Invest. 2020;100:738–50. https://doi.org/10.1038/s41374-019-0364-0.
308. McIlvried LA, Atherton MA, Horan NL, Goch TN, Scheff NN. Sensory neurotransmitter calcitonin gene-related peptide modulates tumor growth and lymphocyte infiltration in oral squamous cell carcinoma. Adv Biol (Weinh). 2022;6:e2200019. https://doi.org/10.1002/adbi.202200019.
309. Toda M, et al. Neuronal system-dependent facilitation of tumor angiogenesis and tumor growth by calcitonin gene-related peptide. Proc Natl Acad Sci U S A. 2008;105:13550–5. https://doi.org/10.1073/pnas.0800767105.
310. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev. 2007;87:873–904. https://doi.org/10.1152/physrev.00041.2006.
311. Herman JP, et al. Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. Compr Physiol. 2016;6:603–21. https://doi.org/10.1002/cphy.c150015.
312. Mohammadpour H, et al. beta2 adrenergic receptor-mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells. J Clin Invest. 2019;129:5537–52. https://doi.org/10.1172/JCI129502.
313. Mohammadpour H, MacDonald CR, McCarthy PL, Abrams SI, Repasky EA. beta2-adrenergic receptor signaling regulates metabolic pathways critical to myeloid-derived suppressor cell function within the TME. Cell Rep. 2021;37:109883. https://doi.org/10.1016/j.celrep.2021.109883.
314. Kokolus KM, et al. Stressful presentations: mild cold stress in laboratory mice influences phenotype of dendritic cells in naive and tumor-bearing mice. Front Immunol. 2014;5:23. https://doi.org/10.3389/fimmu.2014.00023.
315. Kokolus KM, et al. Baseline tumor growth and immune control in laboratory mice are significantly influenced by subthermoneutral housing temperature. Proc Natl Acad Sci U S A. 2013;110:20176–81. https://doi.org/10.1073/pnas.1304291110.
316. Rosenne E, et al. In vivo suppression of NK cell cytotoxicity by stress and surgery: glucocorticoids have a minor role compared to catecholamines and prostaglandins. Brain Behav Immun. 2014;37:207–19. https://doi.org/10.1016/j.bbi.2013.12.007.
317. Goldfarb Y, et al. Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses. Ann Surg. 2011;253:798–810. https://doi.org/10.1097/SLA.0b013e318211d7b5.
318. Nissen MD, Sloan EK, Mattarollo SR. beta-Adrenergic Signaling Impairs Antitumor CD8(+) T-cell Responses to B-cell Lymphoma Immunotherapy. Cancer Immunol Res. 2018;6:98–109. https://doi.org/10.1158/2326-6066.CIR-17-0401.
319. Qiao G, et al. Chronic Adrenergic Stress Contributes to Metabolic Dysfunction and an Exhausted Phenotype in T Cells in the Tumor Microenvironment. Cancer Immunol Res. 2021;9:651–64. https://doi.org/10.1158/2326-6066.CIR-20-0445.
320. He XY et al. Chronic stress increases metastasis via neutrophil-mediated changes to the microenvironment. Cancer Cell 2024. https://doi.org/10.1016/j.ccell.2024.01.013
321. Kokolus KM, et al. Beta blocker use correlates with better overall survival in metastatic melanoma patients and improves the efficacy of immunotherapies in mice. Oncoimmunology. 2018;7:e1405205. https://doi.org/10.1080/2162402X.2017.1405205.
322. Fjaestad KY, et al. Blockade of beta-adrenergic receptors reduces cancer growth and enhances the response to anti-CTLA4 therapy by modulating the tumor microenvironment. Oncogene. 2022;41:1364–75. https://doi.org/10.1038/s41388-021-02170-0.

323. Zhang Z, Lv ZG, Lu M, Li H, Zhou J. Nerve-tumor crosstalk in tumor microenvironment: From tumor initiation and progression to clinical implications. Biochim Biophys Acta Rev Cancer. 2024;1879:189121. https://doi.org/10.1016/j.bbcan.2024.189121.
324. Zhang Z, et al. Electroacupuncture regulates inflammatory cytokines by activating the vagus nerve to enhance antitumor immunity in mice with breast tumors. Life Sci. 2021;272:119259. https://doi.org/10.1016/j.lfs.2021.119259.
325. Renz BW, et al. Cholinergic signaling via muscarinic receptors directly and indirectly suppresses pancreatic tumorigenesis and cancer stemness. Cancer Discov. 2018;8:1458–73. https://doi.org/10.1158/2159-8290.CD-18-0046.
326. Tan KP, Talaulikar D, Scholz B. Factors of emotional distress in lymphoma: A systematic review. Cancer Med. 2023;12:14646–62. https://doi.org/10.1002/cam4.6069.
327. Zeng Y, et al. Association between pretreatment emotional distress and immune checkpoint inhibitor response in non-small-cell lung cancer. Nat Med. 2024;30:1680–8. https://doi.org/10.1038/s41591-024-02929-4.
328. Hathaway CA, et al. The relationship of lifetime history of depression on the ovarian tumor immune microenvironment. Brain Behav Immun. 2023;114:52–60. https://doi.org/10.1016/j.bbi.2023.08.006.
329. Kuczmarski TM, Roemer L, Odejide OO. Depression in patients with hematologic malignancies: The current landscape and future directions. Blood Rev. 2024;65:101182. https://doi.org/10.1016/j.blre.2024.101182.
330. Curtis AM, Bellet MM, Sassone-Corsi P, O'Neill LA. Circadian clock proteins and immunity. Immunity. 2014;40:178–86. https://doi.org/10.1016/j.immuni.2014.02.002.
331. Man K, Loudon A, Chawla A. Immunity around the clock. Science. 2016;354:999–1003. https://doi.org/10.1126/science.aah4966.
332. Wang C, Lutes LK, Barnoud C, Scheiermann C. The circadian immune system. Sci Immunol. 2022;7:eabm2465. https://doi.org/10.1126/sciimmunol.abm2465.
333. Wang C, et al. Dendritic cells direct circadian anti-tumour immune responses. Nature. 2023;614:136–43. https://doi.org/10.1038/s41586-022-05605-0.
334. Wang C, et al. Circadian tumor infiltration and function of CD8(+) T cells dictate immunotherapy efficacy. Cell. 2024;187:2690-2702 e2617. https://doi.org/10.1016/j.cell.2024.04.015.
335. Fortin BM et al. Circadian control of tumor immunosuppression affects efficacy of immune checkpoint blockade. Nat Immunol 2024. https://doi.org/10.1038/s41590-024-01859-0
336. Alizadeh S, Esmaeili A, Barar J, Omidi Y. Optogenetics: A new tool for cancer investigation and treatment. Bioimpacts 2022;12:295–299. https://doi.org/10.34172/bi.2021.22179
337. Zhang K, et al. Light-mediated kinetic control reveals the temporal effect of the Raf/MEK/ERK pathway in PC12 cell neurite outgrowth. PLoS One. 2014;9:e92917. https://doi.org/10.1371/journal.pone.0092917.
338. Idevall-Hagren O, Dickson EJ, Hille B, Toomre DK, De Camilli P. Optogenetic control of phosphoinositide metabolism. Proc Natl Acad Sci U S A. 2012;109:E2316-2323. https://doi.org/10.1073/pnas.1211305109.
339. Malogolovkin A, Egorov AD, Karabelsky A, Ivanov RA, Verkhusha VV. Optogenetic technologies in translational cancer research. Biotechnol Adv. 2022;60:108005. https://doi.org/10.1016/j.biotechadv.2022.108005.
340. Kielbus M, et al. Optogenetics in cancer drug discovery. Expert Opin Drug Discov. 2018;13:459–72. https://doi.org/10.1080/17460441.2018.1437138.
341. Schiller M, et al. Optogenetic activation of local colonic sympathetic innervations attenuates colitis by limiting immune cell extravasation. Immunity. 2021;54:1022-1036 e1028. https://doi.org/10.1016/j.immuni.2021.04.007.
342. Wang Y et al. Affinity fine-tuning anti-CAIX CAR-T cells mitigate on-target off-tumor side effects. Mol Cancer 2024;23. https://doi.org/10.1186/s12943-024-01952-w
343. Cattaruzza F, et al. Precision-activated T-cell engagers targeting HER2 or EGFR and CD3 mitigate on-target, off-tumor toxicity for immunotherapy in solid tumors. Nat Cancer. 2023;4:485–501. https://doi.org/10.1038/s43018-023-00536-9.
344. Huang K, Liu X, Han G, Zhou Y. Nano-optogenetic immunotherapy. Clin Transl Med 2022;12. https://doi.org/10.1002/ctm2.1020
345. Nguyen NT, et al. Nano-optogenetic engineering of CAR T cells for precision immunotherapy with enhanced safety. Nat Nanotechnol. 2021;16:1424–34. https://doi.org/10.1038/s41565-021-00982-5.
346. Li Y, et al. Immunotherapy as a treatment for Stroke: Utilizing regulatory T cells. Brain Hemorrhages. 2023;4:147–53. https://doi.org/10.1016/j.hest.2023.02.003.
347. Fallon M, et al. A randomized placebo-controlled trial of the anti-nerve growth factor antibody tanezumab in subjects with cancer pain due to bone metastasis. Oncologist. 2023;28:e1268–78. https://doi.org/10.1093/oncolo/oyad188.
348. Avallone A, et al. Randomized phase II study of valproic acid in combination with bevacizumab and oxaliplatin/fluoropyrimidine regimens in patients with RAS-mutated metastatic colorectal cancer: the REVOLUTION study protocol. Ther Adv Med Oncol. 2020;12:1758835920929589. https://doi.org/10.1177/1758835920929589.
349. Kline CL, et al. ONC201 kills solid tumor cells by triggering an integrated stress response dependent on ATF4 activation by specific eIF2alpha kinases. Sci Signal. 2016;9:ra18. https://doi.org/10.1126/scisignal.aac4374.
350. Free RB, et al. Pharmacological characterization of the imipridone anticancer Drug ONC201 reveals a negative allosteric mechanism of action at the D(2) dopamine receptor. Mol Pharmacol. 2021;100:372–87. https://doi.org/10.1124/molpharm.121.000336.
351. Ishizawa J, et al. Mitochondrial ClpP-mediated proteolysis induces selective cancer cell lethality. Cancer Cell. 2019;35:721-737 e729. https://doi.org/10.1016/j.ccell.2019.03.014.
352. Madhukar NS, et al. A Bayesian machine learning approach for drug target identification using diverse data types. Nat Commun. 2019;10:5221. https://doi.org/10.1038/s41467-019-12928-6.
353. Chi AS, et al. Pediatric and adult H3 K27M-mutant diffuse midline glioma treated with the selective DRD2 antagonist ONC201. J Neurooncol. 2019;145:97–105. https://doi.org/10.1007/s11060-019-03271-3.
354. Arrillaga-Romany I, et al. ONC201 (Dordaviprone) in recurrent H3 K27M-mutant diffuse midline glioma. J Clin Oncol. 2024;42:1542–52. https://doi.org/10.1200/JCO.23.01134.
355. Anderson PM, et al. Phase II Study of ONC201 in Neuroendocrine tumors including pheochromocytoma-paraganglioma and desmoplastic small round cell tumor. Clin Cancer Res. 2022;28:1773–82. https://doi.org/10.1158/1078-0432.CCR-21-4030.
356. Ray JE, et al. Antitumorigenic effect of combination treatment with ONC201 and TRAIL in endometrial cancer in vitro and in vivo. Cancer Biol Ther. 2021;22:554–63. https://doi.org/10.1080/15384047.2021.1977067.
357. Atkins SLP, et al. A single-arm, open-label phase II study of ONC201 in recurrent/refractory metastatic breast cancer and advanced endometrial carcinoma. Oncologist. 2023;28:919-e972. https://doi.org/10.1093/oncolo/oyad164.
358. Munson JM, et al. Anti-invasive adjuvant therapy with imipramine blue enhances chemotherapeutic efficacy against glioma. Sci Transl Med. 2012;4:127ra136. https://doi.org/10.1126/scitranslmed.3003016.
359. Rajamanickam S, et al. Inhibition of FoxM1-mediated DNA repair by imipramine blue suppresses breast cancer growth and metastasis. Clin Cancer Res. 2016;22:3524–36. https://doi.org/10.1158/1078-0432.CCR-15-2535.
360. Musazzi L, et al. Acute stress increases depolarization-evoked glutamate release in the rat prefrontal/frontal cortex: the dampening action of antidepressants. PLoS One. 2010;5:e8566. https://doi.org/10.1371/journal.pone.0008566.
361. Popoli M, Yan Z, McEwen BS, Sanacora G. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. Nat Rev Neurosci. 2011;13:22–37. https://doi.org/10.1038/nrn3138.
362. Grytli HH, Fagerland MW, Fossa SD, Tasken KA, Haheim LL. Use of beta-blockers is associated with prostate cancer-specific survival in prostate cancer patients on androgen deprivation therapy. Prostate. 2013;73:250–60. https://doi.org/10.1002/pros.22564.
363. Powe DG, Entschladen F. Targeted therapies: Using beta-blockers to inhibit breast cancer progression. Nat Rev Clin Oncol. 2011;8:511–2. https://doi.org/10.1038/nrclinonc.2011.123.
364. Lemeshow S, et al. beta-Blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. Cancer Epidemiol Biomarkers Prev. 2011;20:2273–9. https://doi.org/10.1158/1055-9965.EPI-11-0249.
365. Udumyan R, et al. Beta-blocker drug use and survival among patients with pancreatic adenocarcinoma. Cancer Res. 2017;77:3700–7. https://doi.org/10.1158/0008-5472.CAN-17-0108.

366. Gandhi S, et al. Phase I clinical trial of combination propranolol and pembrolizumab in locally advanced and metastatic melanoma: safety, tolerability, and preliminary evidence of antitumor activity. Clin Cancer Res. 2021;27:87–95. https://doi.org/10.1158/1078-0432.CCR-20-2381.
367. Kennedy OJ, et al. Prognostic and predictive value of beta-blockers in the EORTC 1325/KEYNOTE-054 phase III trial of pembrolizumab versus placebo in resected high-risk stage III melanoma. Eur J Cancer. 2022;165:97–112. https://doi.org/10.1016/j.ejca.2022.01.017.

Publisher's Note