

Perspective



The neural addiction of cancer

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Abstract

The recently uncovered key role of the peripheral and central nervous systems in controlling tumorigenesis and metastasis has opened a new area of research to identify innovative approaches against cancer. Although the 'neural addiction' of cancer is only partially understood, in this Perspective we discuss the current knowledge and perspectives on peripheral and central nerve circuitries and brain areas that can support tumorigenesis and metastasis and the possible reciprocal influence that the brain and peripheral tumours exert on one another. Tumours can build up local autonomic and sensory nerve networks and are able to develop a long-distance relationship with the brain through circulating adipokines, inflammatory cytokines, neurotrophic factors or afferent nerve inputs, to promote cancer initiation, growth and dissemination. In turn, the central nervous system can affect tumour development and metastasis through the activation or dysregulation of specific central neural areas or circuits, as well as neuroendocrine, neuroimmune or neurovascular systems. Studying neural circuitries in the brain and tumours, as well as understanding how the brain communicates with the tumour or how intratumour nerves interplay with the tumour microenvironment, can reveal unrecognized mechanisms that promote cancer development and progression and open up opportunities for the development of novel therapeutic strategies. Targeting the dysregulated peripheral and central nervous systems might represent a novel strategy for next-generation cancer treatment that could, in part, be achieved through the repurposing of neuropsychiatric drugs in oncology.

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Introduction

The discovery of the nervous system as a key player in cancer initiation and progression represents a new paradigm shift in oncology^{1,2}. The nervous system is found throughout the body and can participate in the regulation of all organs that are locally innervated by peripheral nerves and are controlled by the brain, the central neural regulator of the whole body. The first indication of a role for the nervous system in cancer can be traced back to ~400 BC, when Hippocrates and Galen proposed a potential link between cancer and depression, which they called melancholia, referring to the excess of black bile in the body^{3,4}. However, the black bile theory was abandoned over the subsequent centuries and the role of the nervous system in oncology was neglected for decades. Although towards the end of the nineteenth century Paget laid the foundation of research on the tumour microenvironment (TME)⁵ by defining the seed and soil theory⁶, which was supported by the discovery that tumour neo-angiogenesis⁷ along with adaptive and innate immunity were involved in tumour formation, the potential role of nerves in the TME was essentially left behind.

Only recently, the role of nerve fibres or neural cells in the TME has started to be elucidated. For example, perineural invasion, the process by which cancer cells surround and infiltrate nerves, has been associated with tumour aggressiveness and tumour-associated pain^{8,9}. In addition, the overexpression of neurotrophic growth factors, such as nerve growth factor (NGF) in tumours^{10–12}, also suggested that neural signalling can affect cancer, and research on the role of psychological stress in cancer implied that the brain might participate in tumorigenesis^{13–17}. However, a turning point was reached in 2013, with the first demonstration in mouse models of prostate cancer that nerve fibres could sprout into tumour tissues through the process of axonogenesis, where they could contribute to cancer growth and dissemination¹⁸. This discovery was soon after confirmed in gastric cancer¹⁹ and was followed by several studies in gastric²⁰, skin²¹, pancreatic^{22–25} and breast^{26,27} cancer, all of which demonstrated that tumour tissues are infiltrated by autonomic or sensory nerve fibres that release neurotransmitters capable of binding their cognate receptors, which are expressed in stromal and cancer cells (previously reviewed in refs. 28–30). Therefore, more than 2,000 years after Hippocrates and Galen, a link between cancer and the nervous system was re-introduced and the novel field of cancer neuroscience emerged¹.

Cancer neuroscience aims to decipher the crosstalk between the nervous system and cancer, providing a new perspective on how cancer develops and progresses, thereby offering new ideas for innovative therapies. Although the field has mainly focused on the role of peripheral nerves in the TME^{28–30}, growing evidence points to a convergence of the peripheral and central nervous system (CNS), and to the involvement of the brain in particular, as previously reviewed³¹, making central and peripheral neural wirings one joint neural system committed to the tumour. In this Perspective, we review the neural addiction of cancer with a particular emphasis on the bidirectional crosstalk between the brain and the tumour. We detail specific aspects of this emerging field to understand the possible control loop that connects the TME with certain brain areas to affect the development and progression of cancer, and discuss the ongoing clinical trials that support the possible repurposing of neuropsychiatric drugs in oncology.

How the brain teams up with the tumour

Involvement of brain areas in cancer development

Inputs from the brain drive the physiological function of organs and maintain homeostasis throughout life³². There is now evidence that

alteration of specific brain areas or dysregulation of central neural circuitries can affect homeostasis and impact tumorigenesis and metastasis (Fig. 1). Although, for clarity, we will describe the involvement of the different brain areas separately, it is important to note that they are not isolated but are rather intertwined by direct and indirect neuronal connections.

The PVN of the hypothalamus and the pituitary gland. The paraventricular nucleus (PVN) of the hypothalamus, a brain area adjacent to the third ventricle, is an important autonomic control centre in the brain, with neurons playing essential roles in various processes such as the control of stress, metabolism, growth and immunity. In the mid-twentieth century, intriguing studies suggested that psychological stress, including distress, social changes or physical harm, or psychiatric disorders, such as depression or schizophrenia, increased the incidence and development of various tumour types in rodent cancer models. These tumours were associated with poor survival of the rodents if the body had failed to adapt to or cope with repeated exposure to intense stressors before tumour onset^{13–17}; however, the underlying mechanisms controlling these events were unclear at the time. It was only speculated that stress activates the hypothalamic–pituitary–adrenal (HPA) axis, which is involved in producing blood-borne glucocorticoids that, in turn, decrease the immunological control of cancer cells (Figs. 1 and 2). This theory has only recently been confirmed when glucocorticoids were shown to control the dissemination of breast cancer cells in orthotopic xenograft models³³. Activation of neuroendocrine neurons that are located in the dorsomedial parvocellular division of the PVN regulates the physiological circadian release of glucocorticoids by the adrenal cortex and also modulates glucocorticoid production and release under stress conditions^{34,35} (Figs. 1 and 2). As a result, high levels of glucocorticoids in the plasma were shown to induce the activation of glucocorticoid receptors on tumour cells of distant metastases and to cause thymic involution and a reduction in the number of circulating T cells, which accelerated tumour growth and dissemination^{15,33}. Besides chronic stress, levels of glucocorticoids were elevated in the blood of patients with breast cancer and rhythms of secretion were disturbed when a tumour developed in the periphery, suggesting that the HPA axis can be altered by metastasis³³; this was also shown in breast cancer patient-derived xenograft models³³.

Beyond the HPA axis, the sympatho-adrenal system (SAS) is known to control the production and secretion of the catecholamines epinephrine (also known as adrenaline) and norepinephrine (also known as noradrenaline) by the adrenal medulla into the bloodstream under stress conditions³⁶ (Figs. 1 and 2). Involvement of the SAS in cancer was first shown in an orthotopic ovarian cancer xenograft model when mice were subjected to stressors such as physical restraint or isolation. In this model, inhibition of the β-adrenergic pathway blocked tumour growth although the HPA axis was still active³⁷. Interestingly, interaction of both neuroendocrine axes can amplify their effects on cancer either by regulating each other or by being modulated by distinct adrenergic signalling pathways in the CNS^{38–40}. Specifically, in the SAS, the adrenal medulla has been shown to be controlled by the adrenoregic splanchnic division of the sympathetic nervous system originating in the CNS (Figs. 1 and 2), whereas the PVN-regulated HPA axis can be activated through the release of catecholamines by noradrenergic neurons of the nucleus of the solitary tract^{41,42} or the locus coeruleus–noradrenergic system in the brainstem³⁴ (Fig. 2). Nevertheless, total resection of the adrenal gland and consequently the abrogation of the HPA axis or the SAS do not prevent stress-induced development of

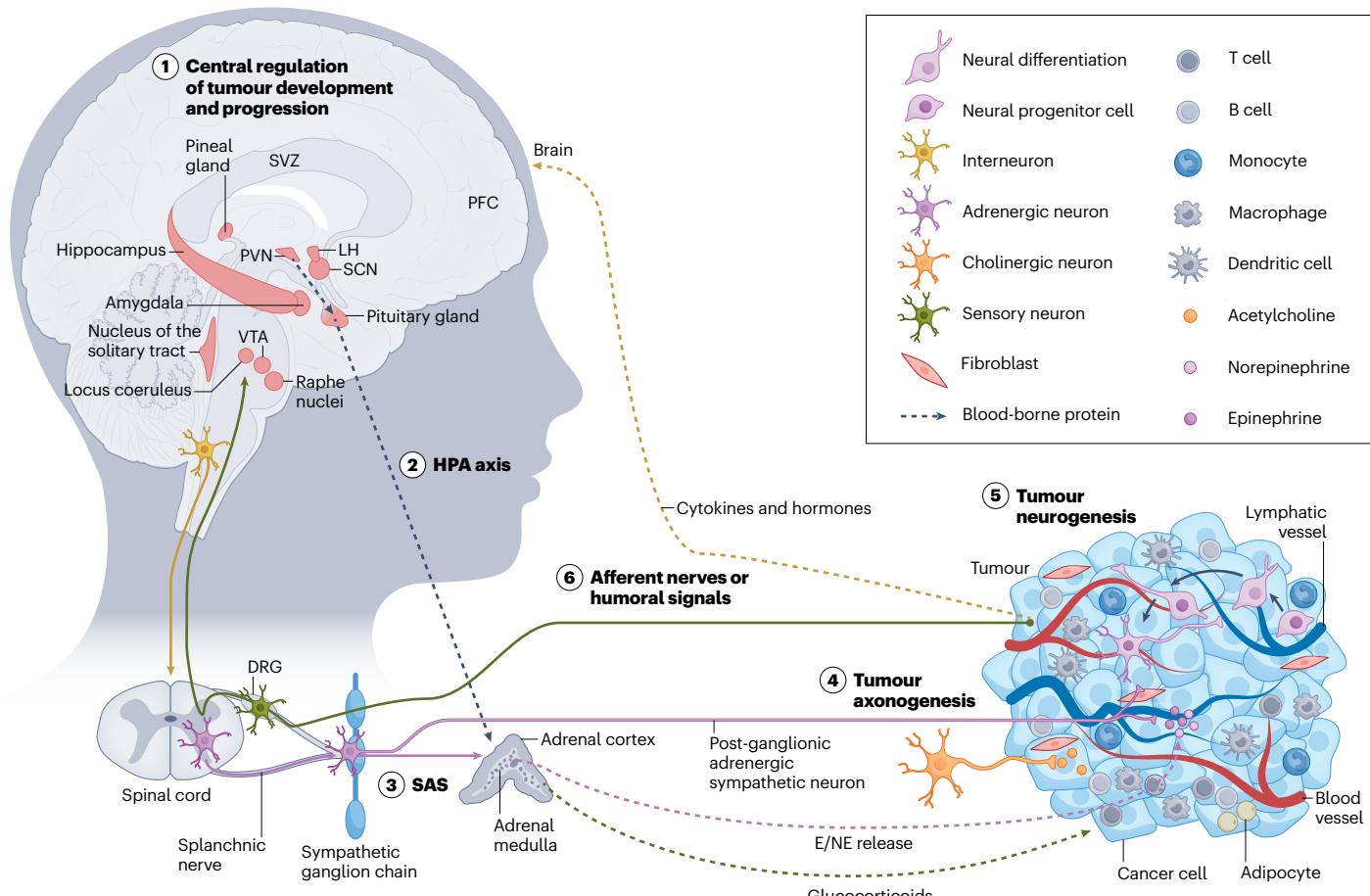


Fig. 1 | Bidirectional crosstalk between the nervous system and solid tumours.

Specific brain areas, including the subventricular zone (SVZ), paraventricular nucleus (PVN) of the hypothalamus, lateral hypothalamus (LH), suprachiasmatic nucleus (SCN), pituitary gland, raphe nuclei, ventral tegmental area (VTA), nucleus of the solitary tract, locus coeruleus, pineal gland, amygdala, hippocampus and prefrontal cortex (PFC), indirectly connect with solid tumours and support their development (1). Efferent neural inputs from the brain can travel through central neuroendocrine systems such as the hypothalamic–pituitary–adrenal (HPA) axis (2) or the sympatho–adrenal system (SAS) (3). Besides central neuroendocrine

systems, tumours generate their own autonomic nerve network through the outgrowth of pre-existing adrenergic or cholinergic nerve fibres in a process known as tumour axonogenesis (4) to regulate cancer cells and other components of the tumour microenvironment. Meanwhile, the process of tumour neurogenesis occurs (5), by which neural progenitors differentiate to form adrenergic neurons in the tumour microenvironment. The tumour in turn can indirectly connect with the brain through afferent sensory nerve fibres or the secretion of cytokines and hormones (6). DRG, dorsal root ganglia; E, epinephrine (also known as adrenaline); NE, norepinephrine (also known as noradrenaline).

syngeneic murine adenocarcinomas, suggesting that these neuroendocrine axes were not the sole mechanism by which the brain participates in the regulation of cancer⁴³. The PVN of the hypothalamus in general appears to be pivotal in the interplay with cancer as it is highly innervated by various neural populations that are in turn controlled by neural projections coming from diverse brain areas. These areas include the nucleus of the solitary tract, suprachiasmatic nucleus (SCN), lateral hypothalamus (LH), amygdala, hippocampus and prefrontal cortex (PFC), all of which have been shown to be involved in regulating cancer as will be described below³⁴ (Figs. 1 and 2).

The PFC, amygdala and hippocampus. The PFC, hippocampus and amygdala are involved in modulating cognitive processes, emotions, and behaviour and are disrupted in patients with cognitive decline or psychiatric diseases⁴⁴. Cognitive decline has been reported in

treatment-naive patients with breast or colon cancer^{45,46}, which was partially attributed to the stress related to suffering from the disease^{47–50}. Along this line, alterations of some brain areas, such as atrophy of the hippocampus coinciding with a functional deficit of episodic autobiographical memory retrieval in patients with breast cancer, have also been reported^{51,52}. Whereas the CNS is pivotal in the adaptation to psychological stress through activation of the neuroendocrine axes, the brain architecture itself can also be remodelled as a consequence of intense stress that is experienced throughout the lifespan. Hence, the PFC, amygdala and hippocampus can be altered by chronic stress or chronic administration of glucocorticoids causing alteration of neuronal structures or dendritic remodelling^{53–58}.

It was further suggested that stress can cause cognitive impairment and neuropsychiatric disorders by affecting glutamatergic neurotransmission in the PFC, amygdala or hippocampus, although

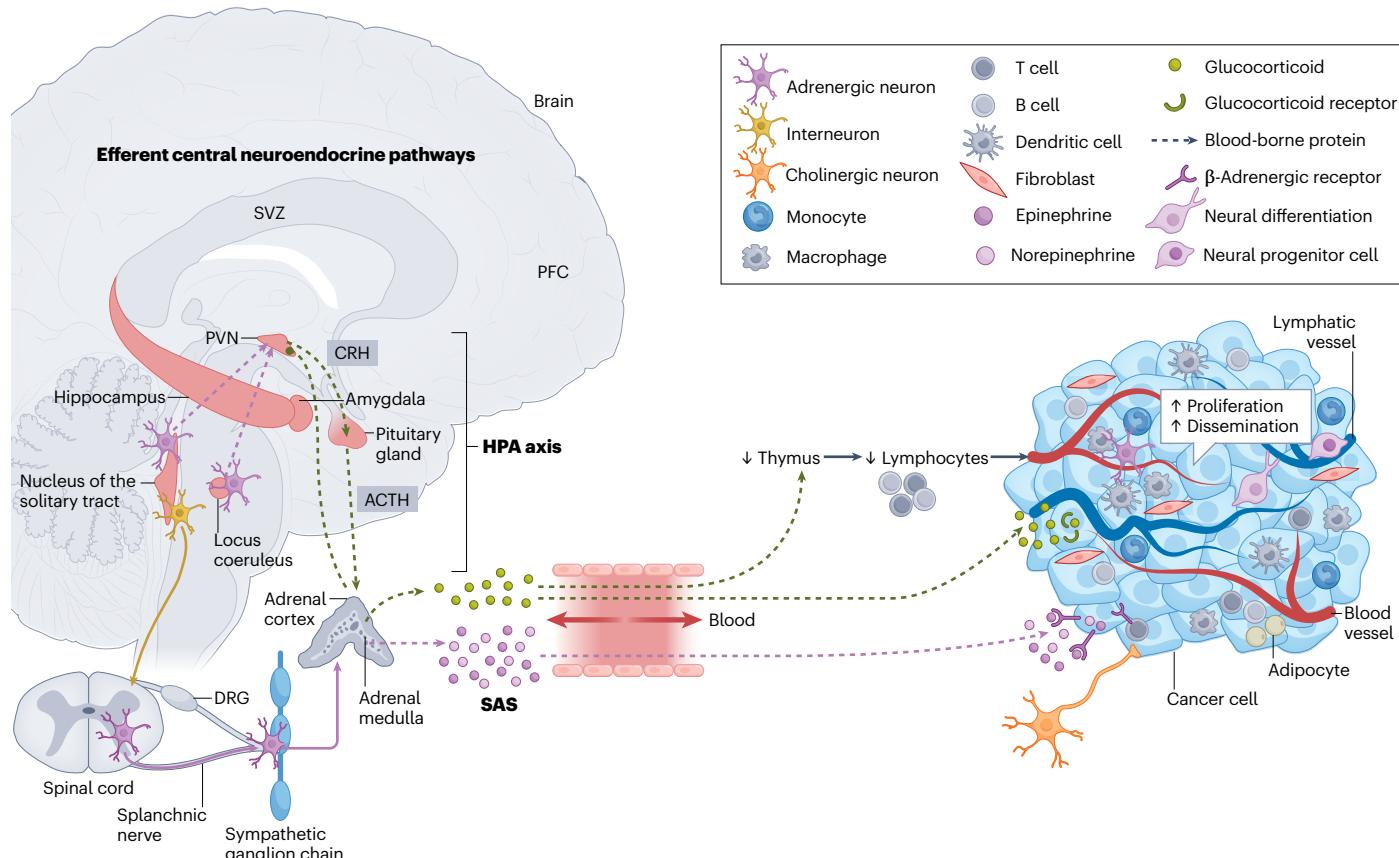


Fig. 2 | Efferent central neuroendocrine pathways controlling tumour

development and progression. Upon activation of the hypothalamic–pituitary–adrenal (HPA) axis, corticotropin-releasing hormone (CRH) is secreted by neurons in the paraventricular nucleus (PVN) of the hypothalamus and travels to the anterior pituitary, where it induces the release of the adrenocorticotrophic hormone (ACTH), which subsequently stimulates the production of glucocorticoids by the adrenal cortex and their release into the circulation. Glucocorticoids promote tumour and metastasis growth upon binding to the glucocorticoid receptors in cancer cells as well as decreased immunological control of the tumour through the involution of the thymus and the subsequent decrease of the number of lymphocytes. The HPA axis can be activated through the release of the catecholamines epinephrine and norepinephrine

by noradrenergic neurons of the nucleus of the solitary tract or the locus coeruleus in the brainstem. Conversely, glucocorticoids can shut off the HPA axis by acting back on the PVN to deactivate glucocorticoid receptor-expressing CRH neurons. Activation of the sympathetic–adrenomedullary system (SAS), in which the splanchnic nerve of the autonomic nervous system receives activating signals from the central nervous system through interneurons and innervates the adrenal medulla to promote the production and secretion of catecholamines into the bloodstream. At the tumour site, these neurotransmitters bind to β -adrenergic receptors expressed on cancer and stromal cells and promote cancer cell proliferation and dissemination. DRG, dorsal root ganglia; PFC, prefrontal cortex; SVZ, subventricular zone.

careful interpretation of the results is warranted as these studies are difficult to control for covariates such as age^{50–64}. Interestingly, beyond stress, neurotransmission by glutamate, which is derived from yet-undefined brain areas, was shown to be co-opted to regulate the progression of gliomas and breast-to-brain metastases^{65–68}. Mechanistically, activation of α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPAR) or N-methyl-D-aspartate receptors (NMDAR) expressed by glioma cells or breast-to-brain metastatic cells leads to tumour growth or in vitro cancer cell proliferation using optogenetic or pharmacological approaches^{65–68}. Interestingly, glutamate is the metabolic precursor for γ -aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain, and medulloblastoma cells have been shown to use GABA transaminase to survive in cerebrospinal fluid and disseminate in the leptomeningeal microenvironment of the brain, highlighting the importance of glutamate and its

derivative neurotransmitters in brain tumours⁶⁹. Additionally, neuroinflammation gene signatures, including glutamate signalling, were shown to foster tumour recurrence and breast-to-brain metastases following treatment with a colony-stimulating factor 1 receptor (CSF1R) inhibitor⁷⁰. In this study, using a xenotransplantation model of breast cancer brain metastasis, the vesicular glutamate transporter (VGLUT1) and the vesicular GABA transporter (VGAT) were shown to be decreased in the inflammatory peritumoural area compared to normal brain, resulting in a shifted VGLUT1-to-VGAT ratio towards a relative excess of excitatory VGLUT1 vesicles⁷⁰. Although investigations are warranted to clarify the precise molecular mechanisms involved, this further points to the involvement of glutamate signalling in tumour progression. These findings highlight how central glutamatergic neurons, which are abundant in the PFC, amygdala and hippocampus, can be involved in cancer.

As a potential therapeutic strategy, repurposing of neuropsychiatric drugs (Table 1), such as the AMPAR antagonists perampanel or talampanel that are used as antiepileptic drugs, was suggested to counteract high levels of glutamate released into the synaptic cleft^{66,68}. Additionally, tricyclic antidepressants, such as imipramine or desipramine, which are well known to inhibit the reuptake of serotonin (also known as 5-hydroxytryptamine (5-HT)) and norepinephrine or to antagonize adrenergic and muscarinic cholinergic receptors, might also abolish excitatory postsynaptic potentials by inhibiting glutamate release in the PFC^{71–73}. Preclinical studies have pointed to the role of tricyclic antidepressants in controlling the growth and spread of glioblastoma or breast tumours as single agents or in combination with conventional chemotherapy^{73,74}, which led to the initiation of a phase I clinical trial to test the effect of imipramine in patients with breast cancer (Table 1).

The SCN of the anterior hypothalamus. The SCN is involved in generating and controlling central and peripheral circadian rhythms associated with various physiological processes such as the control of body temperature, the autonomic nervous system and endocrine system, and sleep–wake cycles^{75–77}. Intriguingly, patients with cancer are more prone to disruptions of their physiological circadian rhythms and associated behaviour modifications, such as anxiety, depressed mood or increased fatigue, either as a direct consequence

of the stress related to the disease or due to alterations in central or peripheral circadian neural control mechanisms⁷⁸. In reverse, chronic disturbance of circadian rhythms can promote several diseases, including cancer^{79–82}. In this context, it has been suggested that night-time exposure to light can favour the development of breast tumours through the dysregulation of the circadian expression of genes regulating immunity or metabolism^{82–85}. Similarly, night-shift work has been associated with increased incidence of prostate, colon or lung cancer^{81,86–88}. These effects can be attributed to the regulation of the central circadian clock in the SCN. At steady-state, photic cues from environmental light-dark cycles are received by the retina and transferred to the SCN mainly through excitatory glutamatergic axonal fibres of the retinohypothalamic tract that trigger cyclic adenosine monophosphate (cAMP) signalling required for the control of the core clock genes within the SCN⁸⁹ (Fig. 3). As a result, the SCN can fine-tune the activity of the PVN of the hypothalamus and adrenal cortex but also regulates several other target organs through efferent neural signals or humoral signals^{90,91} (Fig. 3). Using transgenic mouse models, it has been demonstrated that changes in expression in the central clock genes encoding, for example, period circadian regulator 1 (PER1), PER2, cryptochrome 1 (CRY1), CRY2, or brain and muscle ARNT-like 1 (BMAL1), and subsequent dysregulation of efferent sympathetic innervation of the peripheral clock can activate

Table 1 | Clinical trials of neuropsychiatric drugs in cancer

Neuropsychiatric drug	Study characteristics	Phase	Trial identifier
β-Blockers			
Carvedilol	Carvedilol as a therapy for prostate adenocarcinoma prior to prostatectomy	Phase II	NCT02944201 (ref. 279)
Carvedilol	Carvedilol with chemotherapy in second-line glioblastoma and response of circulating tumour cells	Phase I	NCT03861598 (ref. 280)
Propranolol	Propranolol in combination with PD1 checkpoint inhibitor (pembrolizumab) in stage IIIC–IV melanoma that cannot be removed by surgery	Phase II	NCT03384836 (ref. 281)
Propranolol	Perioperative use of propranolol in combination with the non-steroidal anti-inflammatory drug etodolac in pancreatic cancer	Phase II	NCT03838029 (ref. 282)
Propranolol	Perioperative propranolol in combination with the non-steroidal anti-inflammatory drug etodolac in patients undergoing resection with curative intent for primary colon and rectal cancer	Phase II	NCT03919461 (ref. 283)
Propranolol	Perioperative propranolol vs placebo on gene expression in newly diagnosed breast cancer	Phase II	ACTRN12615000889550 (ref. 284)
Antidepressants			
Imipramine	Tricyclic antidepressants imipramine in oestrogen receptor-positive and triple-negative breast cancer	Phase I	NCT03122444 (ref. 285)
Citalopram, escitalopram, sertraline hydrochloride	Effect of the anti-oestrogenic drug tamoxifen on patients with breast cancer receiving selective serotonin reuptake inhibitors (multicentric)	Phase I	NCT00667121 (ref. 286)
Hypnotics/antiepileptics			
Valproate	Valproate and the tyrosine kinase inhibitor neratinib in advanced solid tumours	Phase II	NCT03919292 (ref. 287)
Valproate	Valproate in combination with bevacizumab, a monoclonal antibody against vascular endothelial growth factor A, and the chemotherapeutic drugs oxaliplatin/fluoropyrimidine in patients with RAS-mutated metastatic colorectal cancer	Phase II	NCT04310176 (ref. 288)
Anti-cholinergic			
Solifenacin	Selective type 3 muscarinic cholinergic receptor (CHRM3) antagonists administered to primarily treat hormonal therapy-induced hot flashes in breast cancer	Phase II	NCT01530373 (ref. 289)
Analgesic			
Tanezumab	Neutralizing anti-nerve growth factor (anti-NGF) antibody tanezumab tested to decrease cancer-induced pain in metastatic disease	Phase III	NCT02609828 (ref. 290)

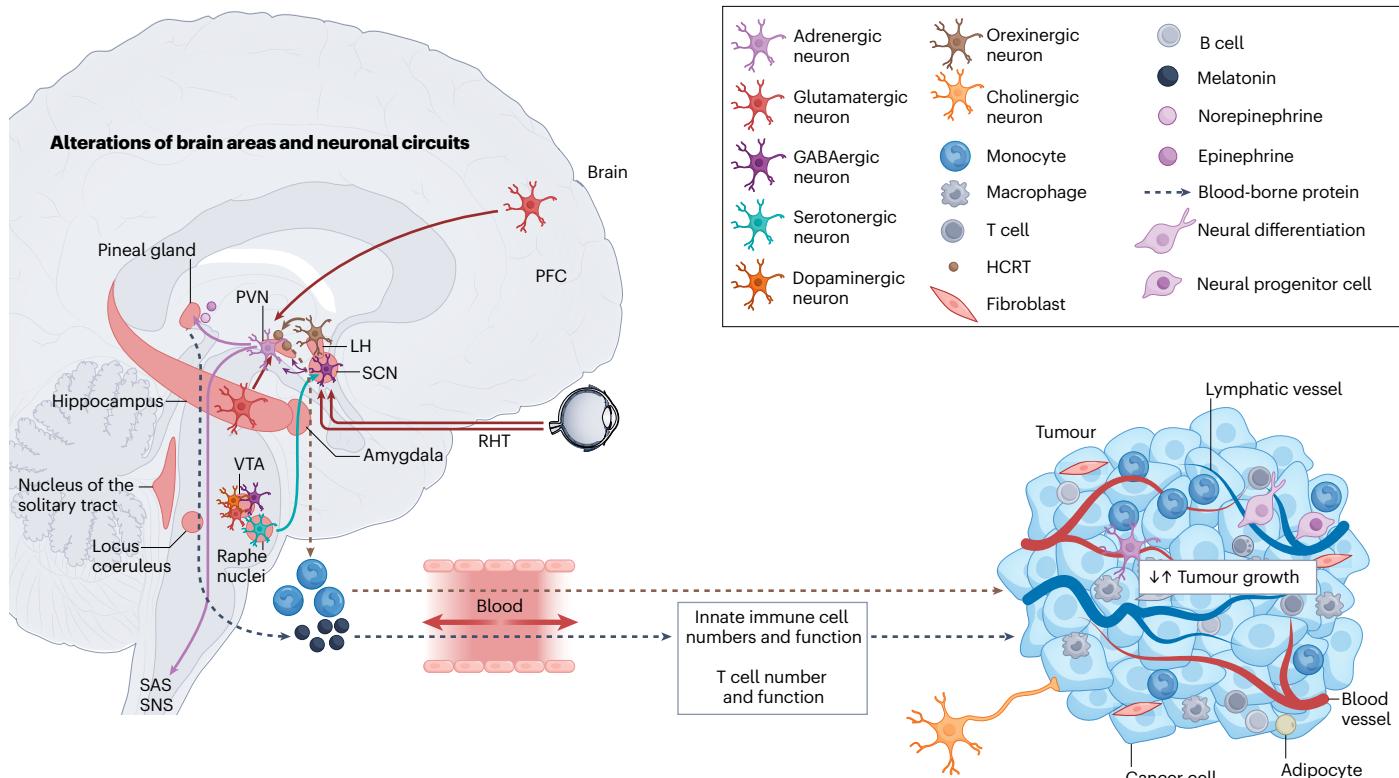


Fig. 3 | Brain areas and circuits participating in tumour development and progression. The brain can promote or sustain tumour development and progression mainly through the hypothalamus, specifically the paraventricular nucleus (PVN), suprachiasmatic nucleus (SCN) or lateral hypothalamus (LH). For instance, glutamatergic projections from the hippocampus or prefrontal cortex (PFC) can act on corticotropin-releasing hormone neurons in the PVN to regulate the hypothalamic–pituitary–adrenal axis. Besides, glutamatergic axonal fibres of the retinohypothalamic tract (RHT) that receive signals from the optic nerve or serotonergic projections of the midbrain raphe nuclei regulate GABAergic projections coming from the SCN to fine-tune PVN function. As a result, adrenergic PVN neurons regulate melatonin secretion from the pineal

gland. Melatonin limits tumour growth through its effects on innate and adaptive immunity and by inhibiting proliferation and increasing apoptosis of cancer cells. Similarly, orexinergic neurons from the LH connect to autonomic PVN neurons through hypocretin (HCRT) secretion to control body functions. Dysregulation of HCRT is involved in regulation of cancer development; for example, a decrease in its level in response to sleep disruption enhances the number of circulating monocytes and their infiltration into the tumour microenvironment. Finally, the rich innervation with dopaminergic, glutamatergic and GABAergic neurons of the midbrain ventral tegmental area (VTA) might also affect the development of peripheral tumours. SAS, sympatho-adrenal system; SNS, sympathetic nervous system.

oncogenic pathways, such as MYC, or block apoptosis in response to DNA damage in tumours of the salivary glands, teratomas around the genital area or lymphomas^{81,92,93}.

Beyond glutamatergic neurotransmission through the retino-hypothalamic tract, the SCN contains multiple populations of neurons or neurotransmitters that actively participate in the regulation of the central and peripheral clocks. Serotonergic projections from the mid-brain raphe nuclei cause modulations of SCN phase shifts in response to light^{94–96} (Fig. 3). Specifically, in rodent models, activation of serotonin receptors can induce phase advances or delays of circadian rhythms^{95,97}. In addition, the neurotransmitter GABA modulates SCN function by inhibiting autonomic neurons in the PVN during the day and by letting them be active at night^{98,99}, which regulates the cyclical secretion of melatonin by the pineal gland, a mechanism that is known to control the sleep–wake pattern^{100,101} (Fig. 3). Circulating melatonin has been shown to stimulate immune responses by binding to melatonin receptors that are expressed on immune cells or by activating the production of inflammatory and immune-stimulatory

cytokines, including IL-1, IL-6, IL-12, tumour necrosis factor (TNF) or interferon-γ (IFNγ), while decreasing anti-inflammatory cytokines such as IL-10 (ref. 102) (Fig. 3). Additionally, melatonin can increase effector T cells and decrease regulatory T cells that are known to block antitumour immunity¹⁰³. Accordingly, reduced secretion of melatonin has been shown to promote cancer development through its effects on innate and adaptive immunity^{83,104–106}. These studies led the International Agency for Research on Cancer (IARC) to classify night-shift work as a probable carcinogen^{107,108}. Therefore, the interplay between the SCN and the autonomic nervous system highlights how the central circadian clock might interact with autonomic innervations, beyond the HPA axis and the SAS, to impact cancer development.

To target disturbed SCN function, the administration of melatonin has been shown to inhibit tumour growth *in vitro* in rat hepatoma and *in vivo* in human breast cancer or leiomyosarcoma xenograft models^{109–112}. Because the phase-shifting effect of light on circadian rhythms can be blocked by glutamate antagonists through the inhibition of field potentials in the SCN^{113–116}, it will be interesting to test,

in animal tumour models, whether this approach could be used to treat cancer. Administration of serotonergic antagonists regulates the sensitivity of the central circadian clock by enhancing phase shifts, supporting the hypothesis that serotonergic innervation from the raphe nuclei, similar to GABA release into the SCN, could adjust glutamatergic inputs in the SCN¹¹⁷. Thus, the outcome of the clinical trial for patients with breast cancer that tests the concomitant administration of hormone therapy with selective inhibitors of serotonin reuptake, primarily used to treat depression (Table 1), will be informative in terms of its effects on tumour growth. In addition, blockade of the 5-HT_{2A} serotonin receptor with the antipsychotic drug pimozide has been shown to inhibit the growth of breast, liver or prostate tumour cells or xenografts by potentially targeting oscillations of central neural pathways in the SCN^{118–121}. Intriguingly, valproic acid, which is primarily used to increase GABA levels by inhibiting GABA transaminase to treat epilepsy or bipolar disorders, is currently being tested in clinical trials to treat patients with gastroenteropancreatic neuroendocrine tumours or recurrent metastatic head and neck squamous cell carcinoma, based on the finding that it also inhibits histone deacetylases, known regulators of tumour suppressor genes^{122,123} (Table 1). However, the antitumour activity of valproic acid might be attributed to its effects on SCN signalling, where it modulates GABA oscillations and increases GABA levels. Non-benzodiazepine GABA-acting hypnotics, such as zolpidem, zopiclone and zaleplon, could also potentially interact with the SCN and disturb the activity of the PVN and, subsequently, of downstream efferent autonomic neurons; however, a retrospective analysis found the use of zolpidem to be associated with increased cancer risk¹²⁴.

The lateral hypothalamus. In addition to the SCN and PVN of the hypothalamus, the lateral part of the hypothalamus and activation of orexinergic neurons have been shown to participate in stimulating the HPA axis in response to psychological stress¹²⁵. Beyond stress, activation of orexinergic neurons in the LH leads to the processing of hypocretin neuropeptide precursors and release of hypocretin 1 (HCRT1, also known as orexin A) and HCRT2 (also known as orexin B), which directly connect to the autonomic sympathetic nervous system to control wakefulness among other body functions^{126–128} (Fig. 3). This control of sleep has been shown to maintain bone marrow homeostasis, while sleep disturbance was shown to decrease HCRT release and enhance circulating monocyte numbers¹²⁹. These monocytes might reach and regulate the tumour immune microenvironment, which could provide a mechanistic explanation for the increased cancer incidence and mortality in patients with altered sleeping behaviour^{130–133}. Indeed, in response to sleep perturbations, tumour growth was increased in a syngeneic lung cancer mouse model, which was mediated by the recruitment of tumour-associated macrophages through activation of the Toll-like receptor 4 (TLR4) inflammatory pathway¹³⁴. Further investigations in syngeneic breast cancer mouse models have shown that aberrant activity of orexinergic neurons in the LH alters sleep and affects glucose metabolism through activation of neural sympathetic circuits¹³⁵ (Fig. 3). Conversely, administration of orexin receptor antagonists or chemical sympathetic denervation of tumour-bearing mice abolished dysregulation of the sleep pattern and glucose metabolism¹³⁵. Therefore, it might be interesting to evaluate whether the dual orexin receptor antagonists suvorexant or almorexant, originally used for the treatment of sleep disturbances¹³⁶, might be capable of blocking the brain–tumour relationship and curbing metabolic changes in patients with cancer¹³⁷.

The midbrain VTA. The midbrain ventral tegmental area (VTA), which plays a role in reward, motivation, cognition and aversion, is particularly rich in dopaminergic neurons. Local brain stimulation through the effect of neuropsychiatric drugs or anaesthesia (for example, barbiturates) or by stereotactic activation of the mesencephalic periaqueductal grey region within the midbrain VTA has been shown to enhance the spread and growth of metastasis in lung or liver tumour models^{138–141}. The VTA and neighbouring substantia nigra are both enriched in dopaminergic neurons, which interact with GABA or glutamate neurons in the VTA to modulate reward-related or goal-directed behaviours¹⁴². These dopamine, glutamate and GABA neurotransmitters sustain normal brain information processing, which is frequently altered in patients with schizophrenia, leading to behaviour and cognitive dysfunction¹⁴³. Patients with schizophrenia also have higher cancer mortality rates, which is commonly attributed to reduced cancer screening and care and the presence of multiple comorbidities^{144,145}. However, another possible reason for this disparity might be the use of neuroleptic medications, such as chlorpromazine or clozapine, that are designed to block D2 dopamine receptors. Because hyperactivity of the dopaminergic system has been demonstrated to inhibit the angiogenesis and growth of mammary tumours implanted into rat models of schizophrenia, it could be hypothesized that the dopaminolytic activity of these neuroleptic medications could promote and enhance tumour initiation and growth^{146,147}. Conversely, genetic activation of VTA dopaminergic neurons using an optogenetic approach prevented the growth of mouse melanoma cells in mice through decreased immunosuppression in response to downregulation of the sympathetic adrenergic innervation of adrenergic receptor-expressing myeloid-derived suppressor cells in the bone marrow, emphasizing the interrelations and complexity of neuronal signalling pathways involved in cancer¹⁴⁸.

The subventricular zone. The subventricular zone (SVZ) is a neurogenic area of the brain located near the lateral ventricles (Fig. 1) that was recently revealed to affect peripheral tumour growth¹⁴⁹. Mechanistically, doublecortin-expressing (DCX⁺) neural progenitors have been shown to leave the SVZ through local permeabilization of the blood-brain barrier (BBB) and circulate in the blood of mice to reach breast or prostate primary tumours or metastases, where they differentiate into adrenergic neo-nerves that support early stages of tumour development¹⁴⁹. In biopsies of human primary prostate tumours, the density of DCX⁺ neural progenitors was strongly associated with tumour aggressiveness, invasiveness and recurrence¹⁴⁹. These findings revealed a novel role of the CNS, as a source of neural progenitors, in the development of peripheral tumours, and exemplified how the central and peripheral nervous systems can cooperate to stimulate the development of cancer. The intriguing role of the permeabilized BBB in the development of distant peripheral tumours¹⁴⁹ was recently echoed by a study showing a distant gut–brain relationship involving inflammatory bowel disease and the vascular barrier in the brain choroid plexus¹⁵⁰.

Downstream neural and non-neural effectors

The aberrant signals originating from the brain areas described above require downstream efferent neural circuitries or endocrine pathways to modulate the development and progression of peripheral tumours.

The adrenal gland. One of these communication routes is through the adrenal gland, which, as part of the HPA axis and SAS, provides a mechanism for the brain to affect other peripheral organs and controls tumour growth and progression via the release of stress hormones,

such as glucocorticoids or catecholamines, into the bloodstream^{33,37} (Figs. 1 and 2). For example, as discussed earlier, increased glucocorticoid release has been demonstrated in breast cancer xenograft mouse models to activate glucocorticoid receptors in distant metastases and reduce survival of tumour-bearing mice³³. Similarly, chronically high levels of circulating catecholamines have been shown to regulate tumour growth in an orthotopic ovarian xenograft model through activation of β 2-adrenergic signalling in cancer cells^{37,151}. Additionally, osteoblasts were found to promote bone colonization of breast cancer cells through stress-induced activation of β 2-adrenergic signalling following stimulation by sympathetic nerves¹⁵². Consequently, non-selective antagonists of β -adrenergic receptors prevented stress-induced bone metastases and, conversely, metastasis formation was enhanced in breast cancer xenograft mouse models by the administration of a selective agonist of the β 2-adrenergic receptor (ADRB2)^{153,154}. An important role of the stress-mediated β 2-adrenergic signalling pathway in cancer progression was also reported in prostate¹⁵⁵, breast^{156,157} and pancreatic¹⁵⁸ cancer; neuroblastoma^{159,160}; and melanoma^{161,162}. Together, these studies indicate the pivotal role of central neuroendocrine stress pathways in cancer.

The autonomic nervous system. Another route of communication between the brain and the tumour can be established through axogenesis¹⁸ (Fig. 1). This phenomenon has been shown to be supported by the local overexpression of neurotrophic growth factors, such as NGF or brain-derived neurotrophic factor (BDNF), in tumour and stromal cells of various cancer types^{10–12,20,24,26,163–165}. The resulting

infiltration of adrenergic sympathetic and cholinergic parasympathetic nerve fibres into the TME has been demonstrated to contribute to tumour initiation and progression through activation of ADRB2 and β 3-adrenergic receptor (ADRB3) or the type 1 or type 3 muscarinic cholinergic receptors (CHRM1 or CHRM3), respectively, expressed on stromal cells^{18,19,24,166,167}. Accordingly, in mouse models of solid tumours, surgical or chemical ablation of nerve fibres or selective blockade of neurotrophic factors expressed in the TME confirmed the importance of axonal nerve outgrowth and local release of neurotransmitters during the development and progression of solid tumours^{18,19,24,164,167}. These processes were consistently found across several types of cancer, truly defining autonomic innervation as a key component of the TME that carries efferent impulses from the brain to the tumour and its micro-environment^{18–20,22,24,26,27,167,168}. Of note, Schwann cells can also participate in building up the tumour nerve network. These cells were found in pancreatic tumours and were associated with pancreatic cancer cells when co-cultured with mouse dorsal root ganglion¹⁶⁹; *in vitro*, factors released by Schwann cells were found to drive the migration of pancreatic cancer cells towards nerves^{170,171}. In addition, the relationship between neuronal activity and cancer cell proliferation in nerve sheath tumours is also of interest as it highlights possible mechanisms regulating the function of Schwann cells in tumorigenesis^{172,173} (Box 1).

Once tumours are innervated, the release of catecholamines activates β -adrenergic receptors, mainly ADRB2 and ADRB3, that are expressed on cancer cells or stromal cells of the TME. In cancer cells, this β -adrenergic signalling has been shown to directly regulate their behaviour by promoting oncogene expression¹⁷⁴, proliferation¹⁷⁵ and invasion¹⁷⁶ but also through inhibition of DNA repair¹⁷⁷, control of survival^{178,179} or programmed cell death^{180,181}. In the TME, adrenergic signalling has been demonstrated to modulate immune responses by recruiting tumour-associated macrophages^{134,153,182} or promoting survival of myeloid-derived suppressor cells that express ADRB2, a key metabolic regulator in these cells¹⁸³. In accordance, genetic disruption of adrenergic nerves or pharmacological blockade of β -adrenergic signalling increased the infiltration of CD8⁺ T cells into the TME and decreased the expression of immune-checkpoint molecules that prevent tumour growth^{27,184,185}. In addition, local autonomic signalling has been found to promote the development of intratumour blood vessels^{37,186–188} and lymphatics¹⁸⁹ required for tumour growth and dissemination. Correspondingly, β -blockers were found to impair tumour angiogenesis in breast and ovarian cancer mouse models and in patients with cancer^{37,190}, and surgical sympathectomy shrank the lymphatic area in the tumour of chemical-induced rat tongue cancer¹⁹¹. Similarly, activation of β -adrenergic signalling in cancer-associated fibroblasts was demonstrated to contribute to tumour angiogenesis through secretion of angiogenic factors or cytokines such as vascular endothelial growth factor A (VEGFA), fibroblast growth factor 2 (FGF2), IL-6 and IL-8 (refs. 192,193). Furthermore, in transgenic mouse models, adrenergic innervation of adipocytes has also been shown to promote cancer through the secretion of adipokines that regulate tumour growth as well as the tumour immune microenvironment, angiogenesis, and cachexia via a hypothalamic brain relay as described below^{194–196}. Finally, β -adrenergic signalling has been implicated in the regulation of epithelial–mesenchymal transition in gastric, pancreatic and colon cancer cell lines^{197–200}. These studies demonstrate that the adrenergic nervous system appears to have a broad impact on various aspects of cancer by providing the brain with a connection route to the tumour. Therefore, blocking β -adrenergic receptors might represent a promising therapeutic strategy as it not only inhibits aberrant signals

Box 1

Relationship between neuronal activity and nerve sheath tumours

Malignant peripheral nerve sheath tumours are a rare type of cancer that originates from Schwann cells and forms at the lining of the nerves that extend from the spinal cord into the body²⁹¹. They often develop in the context of the tumour predisposition syndrome neurofibromatosis 1 (NF1), which is caused by *NF1* mutations²⁹¹. Recently, a study has demonstrated that neuronal hyperexcitability drives central and peripheral nervous system tumour progression in NF1 (ref. 172). In mice with *Nf1* mutations, hyperstimulation of central and peripheral nervous system neurons increased secretion of activity-dependent, tumour-promoting paracrine factors, including the neurofibroma mitogen collagen α -2(I) chain (COL1A2), which increased proliferation of NF1-deficient Schwann cells, thus demonstrating the role of neuronal activity in tumour progression. Additionally, in a mouse model, the purinoreceptor P2RY14, which is expressed in Schwann cells, has recently been shown to participate in the stimulation of neurofibroma formation through cAMP signalling, showing that neuron-mediated purinergic signalling in Schwann cells is dysfunctional in NF1, which might participate in Schwann cell tumourigenesis²⁹².

derived from adrenergic nerve circuits in the brain, such as activation of the PVN, but also limits the effects of catecholamines in the TME. Epidemiological studies indeed suggested that non-selective β 1-blockers and β 2-blockers, such as propranolol or carvedilol, might be effective in improving cancer treatment, as cancer-specific survival of patients with melanoma^{201–203}, pancreatic cancer²⁰⁴, prostate cancer^{205,206}, breast cancer^{207–210}, ovarian cancer²¹¹, colorectal cancer²¹² or non-small-cell lung cancer²¹³ was increased in patients who used β -blockers compared with non-users.

Based on these findings, clinical trials using β -blockers are now being conducted (Table 1), as recently reviewed in ref. 214. In phase II randomized controlled trials involving patients with breast cancer, perioperative or preoperative use of non-selective β -blockers decreased biomarkers and pathways associated with metastasis and increased immune cell infiltration in tumour tissues^{215,216}. In similar trials, propranolol prevented recurrence in adult patients with stage IB to IIIA cutaneous melanoma²¹⁷ and decreased the expression of genes associated with adverse outcomes in patients with haematological malignancies following haematopoietic stem cell transplantation²¹⁸. Multiple trials are ongoing in several types of cancer that are evaluating the effect of β -blockers used in combination with other cancer therapies, including neoadjuvant therapy, PD1 checkpoint inhibitors or non-steroidal anti-inflammatory drugs (Table 1).

In analogy to β -adrenergic nerves, cholinergic nerve fibres have been shown to infiltrate tumour tissues and release acetylcholine, which controls cancer cell dissemination after binding CHRM1 or CHRM3 expressed in the TME^{18–20}. Muscarinic agonists have been shown to activate tumour growth and dissemination, while antagonists of muscarinic receptors blocked metastases or tumorigenesis in transgenic and orthotopic xenograft mouse models of prostate or gastric cancer^{18,19}. However, in pancreatic ductal adenocarcinoma, blocking cholinergic input had the opposite effect and accelerated tumour progression²¹⁹. The results of an ongoing clinical trial evaluating the use of the selective CHRM3 inhibitor solifenacina to treat hormonal therapy-induced hot flashes in patients with breast cancer might be helpful to clarify the role of cholinergic signalling (Table 1).

How peripheral tumours connect with the brain

While the role of the nervous system in tumour development and progression is starting to be elucidated, the impact of the tumour on brain functioning remains enigmatic. Although cognitive disorders, such as distress, anxiety and depression, are frequently reported among patients with cancer²²⁰, these are rarely attributed to a direct effect of the tumour on the brain and are mostly thought to result from the negative psychological impact of knowing to be affected by cancer or are considered to be induced by cancer therapies (Box 2). However, evidence is emerging indicating that tumours might directly regulate brain activities by releasing adipokines, neurotrophic factors, or pro-inflammatory cytokines or through sensory neurons that signal back to the CNS (Fig. 4).

Adipokines and neurotrophic factors

Adipokines, such as leptin, adiponectin and ghrelin, are produced by adipocytes and regulate appetite through binding to specific receptors that are mainly located in the hypothalamus^{221–223}. More precisely, leptin is known to decrease food intake and body weight while increasing energy expenditure, leading to higher levels of adiponectin that control insulin sensitivity through the regulation of lipid and glucose metabolism. In accordance, individuals with obesity display high levels of serum

Box 2

Chemotherapy-related cognitive impairment

Chemotherapy frequently results in a poorly understood syndrome of long-term neurological deficits, such as thinking and memory problems, commonly referred to as chemobrain²⁹³. Mechanistically, dysfunctional interactions of microglia, astrocytes, oligodendrocytes or neurons are thought to contribute to this condition²⁹⁴. In tumour-free mice, chemotherapy was shown to induce perturbation of the brain microenvironment through the activation of inflammatory microglia and astrocytes²⁹⁵. This environmental change led to persistent depletion of oligodendrocyte precursor cells and aberrant and dysfunctional differentiation of oligodendrocytes, resulting in partial myelination. In analogy, depletion of oligodendrocyte lineage cells was also observed in patients with cancer that were treated with chemotherapy²⁹⁶. In addition, the molecular mechanism by which microglia activation leads to chemotherapy-related cognitive impairment (CRCI) seems to be partially resolved²⁹⁵. Using a mouse model of CRCI, it has been shown that methotrexate exposure decreases cortical brain-derived neurotrophic factor (BDNF) expression and that signalling initiated by BDNF after binding to its cognate receptor TRKB seemed to be required for myelination. Depletion of TRKB in oligodendrocyte precursor cells in chemotherapy-naïve mice resulted in impaired cognitive behaviour, while administration of a TRKB agonist restored myelination and cognition²⁹⁵. Identification of these molecular mechanisms might constitute the basis for future targeted treatments designed to rescue the adaptive, activity-dependent myelination that is lost in CRCI.

leptin, develop resistance to leptin, have low adiponectin concentrations and are more prone to developing cancer^{224–227}. Although mainly produced by adipocytes, including cancer-associated adipocytes, leptin or adiponectin and their cognate receptors are also expressed in cancer or stromal cells^{226,228}. These tumour-released adipokines were found to act in a paracrine manner to activate cancer cell proliferation and dissemination and were associated with cancer aggressiveness^{228,229} (Fig. 4). In breast cancer, for instance, the increased expression of leptin and leptin receptors (ObRs) was identified as a marker of tumour progression^{226,230}. In addition to its effect on tumour cells, leptin can increase ObR activation and signalling in brain neurons using the hypothalamic-brain relay^{231,232}. Neurotrophic factors, particularly ciliary neurotrophic factor (CNTF) and BDNF, are also important for the control of body weight by acting in appetite-regulating brain areas such as the hypothalamus, where they act in concert with adipokines²³³.

ObRs are not only expressed in the hypothalamus but also in other brain areas such as the hippocampus and PFC, and ObR-expressing neurons can affect, for instance, VTA dopaminergic neuron activity or LH orexinergic neurons that control tumour initiation, growth and progression through the respective modulation of tumour angiogenesis or immune cell trafficking from the bone marrow^{125,148,223,232} (Fig. 4). Conversely, hypothalamic BDNF-expressing neurons downregulated leptin production in adipocytes, while increasing adiponectin secretion

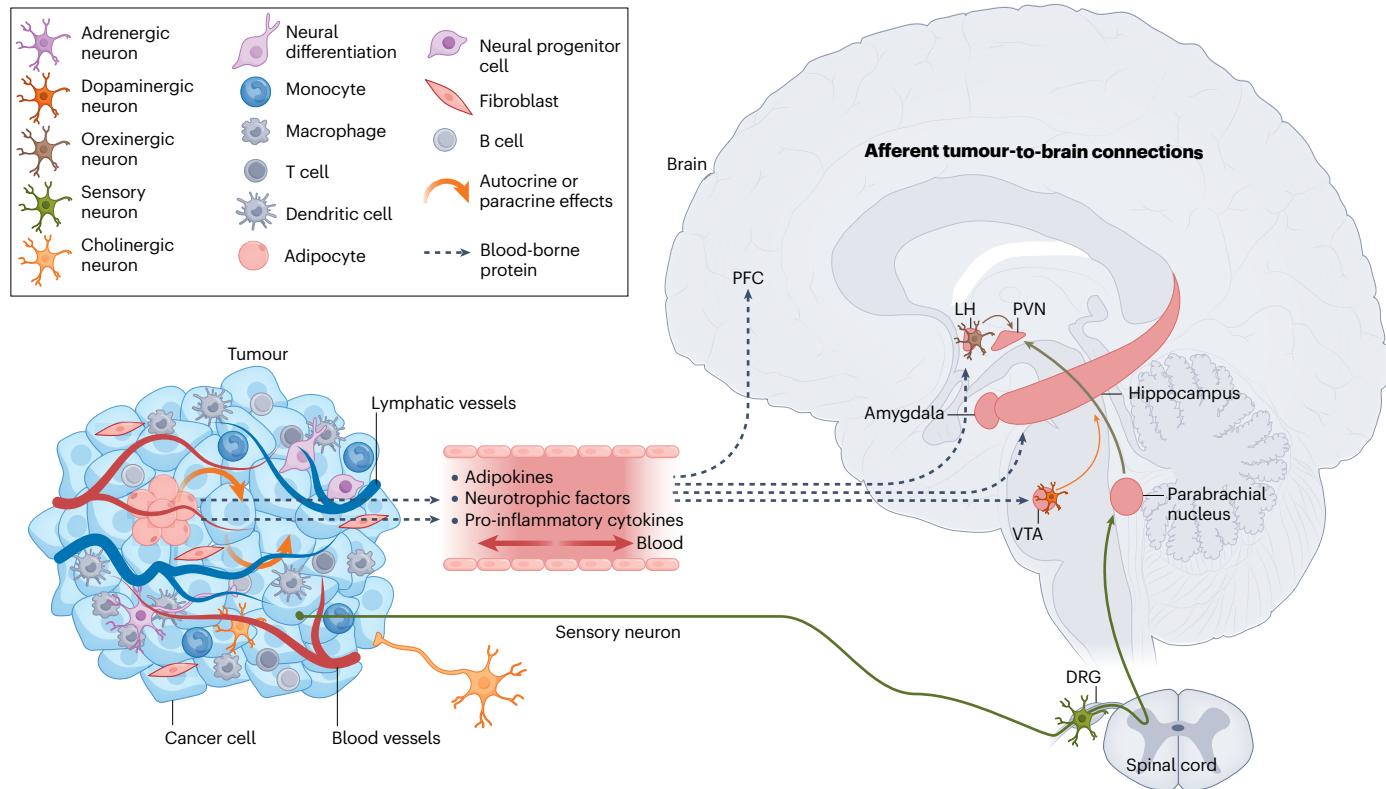


Fig. 4 | Afferent tumour-to-brain connections. Peripheral tumour tissues connect with the brain through the secretion of adipokines, neurotrophic factors and pro-inflammatory cytokines from cancer cells or stromal cells, such as cancer-associated adipocytes, into the bloodstream. These factors reach the brain, where they can dysregulate the activity of the prefrontal cortex (PFC), orexinergic neurons in the lateral hypothalamus (LH), and dopaminergic neurons in the hippocampus and ventral tegmental area (VTA). Additionally, adipocyte-released or cancer cell-released adipokines contribute to cancer cell proliferation

and dissemination in a paracrine or autocrine manner. Sensory innervation of the TME sustains tumour initiation and progression, and can potentially relay information from the tumour to the brain. The parabrachial nucleus works as a sensory relay that receives sensory inputs from the periphery and transfers the information to the hypothalamus and the amygdala, mediating cancer-induced pain, anorexia and cognitive or behavioural disturbances. DRG, dorsal root ganglia; PVN, paraventricular nucleus.

through the activation of the β -adrenergic innervation of adipose tissues, and caused inhibition of cancer cell proliferation and tumour growth in melanoma and colon cancer models¹⁹⁰ (Fig. 4). Interestingly, in mouse models of obesity, a leptin–BDNF pathway has recently been shown to activate the adrenergic innervation of adipose tissue, confirming the role of leptin and hypothalamic BDNF-expressing neurons as regulators of the crosstalk between peripheral tissues and brain areas²³⁴. It should also be mentioned that leptin is likely to be among many tumour-secreted hormones that regulate brain activities. Similar to leptin, adiponectin²²¹ or ghrelin²²² are known regulators of brain activities and are both secreted by tumours^{235–238}; it will be interesting to further investigate the impact of these tumour-derived hormones on the brain and cancer progression.

Pro-inflammatory cytokines

Cognitive impairments, such as memory loss, learning difficulties and lack of concentration, that are frequently observed in patients with cancer have long been considered a side effect of chemotherapy²³⁹; however, it is now acknowledged that patients are affected prior to treatment initiation^{47,48}. During chemotherapy, pro-inflammatory

cytokines, including IL-1 β , IL-2, IL-4, IL-6 or IL-8, were found to be increased in the plasma of patients with cancer and have been shown to be associated with cognitive impairment in patients with cancer²⁴⁰. In addition, elevated levels of pro-inflammatory cytokines were also associated with poor memory prior to treatment in breast tumour-bearing mice²⁴¹. Interestingly, the same study demonstrated that the anti-inflammatory effect of low-dose aspirin blocked tumour-induced memory loss, demonstrating a causal role for inflammation in cognitive impairment. These studies point to the release of pro-inflammatory cytokines into the bloodstream as a potential mechanism by which the tumour could regulate cognitive function (Fig. 4).

Sensory neurons

Innervation of the TME by the peripheral nervous system and the fact that all peripheral nerves are directly or indirectly connected to the CNS, and ultimately the brain, provide a means for the tumour to impact brain activities via nerves. Although the molecular mechanisms remain to be clarified, current data indicate that sensory innervation of the TME stimulates tumour initiation and progression^{21,23,242}. For example, in a mouse model of basal cell carcinoma, it has been

shown that hair follicle stem cells are innervated by sensory nerves, which are required for stem cell proliferation through the activation of hedgehog signalling²¹. The surgical ablation of these nerves leads to the inhibition of tumour initiation, and, although the mechanism is not completely elucidated, these data show that the formation and progression of basal cell carcinomas are dependent on sensory innervation²¹. Similarly, the ablation of sensory neurons in mouse models of pancreatic cancer slowed both the initiation and progression of cancer^{23,242}. Aside from nerve-to-tumour signalling that leads to local stimulation of tumorigenesis, signalling from sensory nerves to the CNS also exists as illustrated by cancer-associated pain²⁴³. This is particularly true for sensory nerves that can propagate afferent signals from the periphery of the body, including stimuli from the tumour or from the external environment, such as odours, sounds, light and touch, to the CNS. For example, some peptidergic PVN innervations arise from viscero-sensory relays and can support activation of the HPA axis in response to visceral disease³⁴. In brain tumours, it has recently been demonstrated that olfactory sensory stimuli can participate in gliomagenesis through the activation of olfactory receptor neurons²⁴⁴.

In this context, cancer-associated pain remains an important clinical issue because it profoundly affects quality of life and patient well-being, and there are currently no drugs available to efficiently treat cancer-associated pain²⁴⁵. Most classic painkillers are quite inefficient on cancer-associated pain, and morphine or its derivatives constitute an imperfect solution as resistance and side effects rapidly overcome the benefit of these drugs²⁴⁶. Targeting calcium signalling might be a promising approach to treat cancer-associated pain as it has been reported to play a major role in nociception by sensing, modulating and integrating neural inputs in the CNS²⁴⁷. Interestingly, activation of calcitonin gene-related peptide (CGRP) sensory neurons in the parabrachial nucleus mediates cancer-induced anorexia and malaise (Fig. 4); in turn, pharmacological and genetic inhibition of CGRP neurons prevented anorexia in mice implanted with Lewis lung carcinoma cells²⁴⁸. These findings establish CGRP neurons as key mediators of cancer-induced appetite suppression and associated behavioural changes, in accordance with the idea that CGRP sensory neurons in the parabrachial nucleus function as a general alarm²⁴⁹. In addition, in mouse models of prostate-to-bone metastasis, blockade of NGF with selective antibodies was found to inhibit sprouting of CGRP sensory nerve fibres in the metastatic microenvironment and to attenuate cancer-associated pain²⁵⁰. A recent study in a mouse model of melanoma has also evidenced that sensory neurons exhibit an immuno-modulatory effect on cytotoxic CD8⁺ T cells through the release of CGRP, suggesting that the inhibition of CGRP signalling in cytotoxic CD8⁺ cells is a potential therapeutic strategy to improve anti-tumour immunity²⁵¹. Thus, deciphering the sensory neural mechanisms leading to cancer-associated pain and changes in brain functioning is warranted, not only to better comprehend the impact of the tumour on brain activities or the development of brain tumours but also to design better therapies to alleviate pain and associated cognitive and behavioural side effects in patients with cancer.

Conclusion and perspectives

Although the role of the nervous system, and in particular the brain, in tumorigenesis and cancer progression has been overlooked, the recent developments described herein show the emergence and rise of the field of cancer neuroscience. Decades earlier, clinical and preclinical observations had suggested that neurotropism through perineural

invasion of some aggressive cancers or dysfunction of the nervous system related to psychological disorders or chronic distress could be involved in controlling cancer incidence, development and progression^{13,15–17,252}. Recent studies have clarified how central neural stress affects hormonal and immunological functions during tumour development and progression^{33,37,153,253}. Trafficking of leukocytes and secretion of inflammatory cytokines have been demonstrated to be perturbed by psychological stress, whereas pharmacological inhibition of adrenergic signalling has been shown to prevent stress-induced dysfunction of the immune system^{254,255}. Furthermore, it has been found that the brain influences tumour tissues that are, in turn, able to respond to the CNS by afferent nerve inputs or humoral signals^{21,23,149,226,256}. Tumour development has been shown to induce cognitive or memory impairments and disruption of the BBB of the SVZ and to induce the secretion of pro-inflammatory cytokines or hormones altering the function of some brain areas^{45,149,241}. In addition, the brain's reward system was implicated in altering adrenergic nerve signalling in the bone marrow that controls the immunosuppressive activity of tumour-infiltrating myeloid-derived suppressor cells¹⁴⁸.

Aside from the brain, tumours are capable of interacting with distant organs to recruit cells that sustain cancer growth and dissemination. For example, an interplay of lung tumours with the bone marrow was identified that leads to the recruitment of a specific subset of neutrophils²⁵⁷. Similarly, gut microbiota have been shown to increase the risk of developing tumours in non-intestinal distal tissues by recruiting myeloperoxidase-positive neutrophils²⁵⁸. These examples clearly demonstrate that such 'long-distance relationships', while underestimated in cancer research, appear to be pivotal to the tumour. This is in accordance with physiological systems that equally require inputs from the brain or other organs, and the understanding of their regulatory circuits could inspire the next steps in cancer research. One such example is the gut and its microbiota or nutrients that interact with the brain using afferent sensory nerve communications to control gastrointestinal physiology^{259–261}. Other examples include the splanchnic nerve, which provides an indirect connection, through the spinal cord, between the PVN or the amygdala and the spleen and controls adaptive immune responses in lymphoid organs²⁶², or adipose tissues that communicate with the brain through activation of the HPA axis²⁶³. All these studies converge towards a novel definition of cancer, establishing it as a potential systemic neural disease.

The local innervation of tumours, through deep infiltration of autonomic or sensory nerve fibres, is now well recognized as a pivotal nerve network that delivers or senses signals required to control the development of tumours. Metastatic cancer cells have also been shown to exploit axon guidance proteins to migrate²⁶⁴. The intratumour neural network could therefore be considered the missing piece of the jigsaw puzzle of the TME and might be involved in orchestrating resistance to cancer therapies.

Understanding the TME has already led to the development of innovative strategies to treat solid tumours^{265,266}, with angiogenesis inhibitors^{267,268} or immunotherapies^{265,266} as prominent examples. Despite initial success, most patients who receive angiogenesis inhibitors or immune-checkpoint inhibitors develop resistance to these therapies, highlighting a yet incomplete understanding of the TME and its crosstalk with cancer cells^{269–272}. Undoubtedly, investigating the peripheral and central neural networks in cancer and targeting these novel selective nerve signalling pathways constitute a promising targeted therapeutic approach, which might also be capable of improving response or overcoming resistance to currently available

Glossary

β-Adrenergic pathway

Intracellular signalling activated by the stimulation of G protein-coupled, β-adrenergic receptors by epinephrine or norepinephrine.

Adipokines

Cytokines secreted by adipose tissue that can function in a paracrine and endocrine manner.

Adrenergic nerves

Nerves for which the neurotransmitter is either epinephrine, norepinephrine, or dopamine.

Adrenergic splanchnic division

Paired autonomic nerves that carry both visceral sympathetic and sensory fibres.

Afferent signals

Neuronal signals carried from the peripheral nervous system to the central nervous system.

Amygdala

Brain area considered as the integrative centre for emotions, emotional behaviour and motivation.

Angiogenesis inhibitors

Compounds that inhibit the growth of new blood vessels.

Astrocytes

Star-shaped and supportive glial cells of the central nervous system.

Autonomic nervous system

Part of the nervous system responsible for the control of bodily functions that are not consciously directed, such as breathing, heartbeat and digestion.

Axonogenesis

Process by which neural extensions, known as axons, are generated. In cancer, tumours build up their own autonomic nerve network through a dynamic axonal outgrowth of pre-existing autonomic nerve fibres in the organ where the tumour initiates.

Calcitonin gene-related peptide

CGRP. Peptide produced by sensory neurons in both the central and peripheral nervous systems that induces dilatation of blood vessels.

Catecholamines

Neurotransmitters produced in the adrenal medulla and the postganglionic fibres of the sympathetic nervous system; the main catecholamines are epinephrine (also known as adrenaline), norepinephrine (also known as noradrenaline) and dopamine.

Cholinergic nerve fibres

Nerve fibres that mainly use acetylcholine as a neurotransmitter.

Efferent neural signals

Neuronal signals carried from the central nervous system to the peripheral nervous system.

Episodic autobiographical memory retrieval

Remembering or re-experiencing a specific personal event from the past.

Field potentials

Transient electrical signals generated in the nervous system.

Glutamatergic neurotransmission

Transmission of information between neurons using glutamate as a neurotransmitter.

Hippocampus

Central brain area that is essential for learning, emotions and memory.

Hypothalamic–pituitary–adrenal (HPA) axis

A neuroendocrine system that mediates glucocorticoid release through molecular interactions among the hypothalamus (a region of the brain located below the thalamus), the pituitary gland (a pea-shaped structure located below the hypothalamus) and the adrenal glands (small conical organs on top of the kidneys).

Immune-checkpoint inhibitors

Drugs used in immunotherapy of cancer to restore the function of the immune system.

Immunotherapies

The treatment of disease by activating or suppressing the immune system.

Lateral hypothalamus

LH. Brain area mainly involved in the regulation of feeding behaviour.

Leptomeningeal microenvironment

Refers to leptomeninges, the two innermost layers of tissue that cover the brain and spinal cord.

Locus coeruleus–noradrenergic system

Cluster of cells in the brainstem that is the main source of the neurotransmitter norepinephrine in the brain.

Mesencephalic periaqueductal grey region

Interface between the forebrain and the lower brainstem that has a role in integrated behavioural responses to internal or external stressors such as pain or threat.

Microglia

A specialized population of phagocytic cells, located in the central nervous system.

Mindfulness-based therapy

A psychotherapeutic approach that uses meditative practices based on awareness of internal thoughts, feelings and emotions.

Muscarinic cholinergic receptors

Membrane protein receptors involved in the transmission of nervous signals in the parasympathetic cholinergic nervous system.

Myelination

Formation of a myelin sheath, which is made of proteins and lipids, around certain nerves, and allows nerve impulses to travel faster.

Nerve fibres

Individual neural extensions also known as axons.

Nerve sheath tumours

Tumours from the cells that form the sheath covering certain peripheral nerves.

Neural cells

Differentiated cells of the nervous system, also called neurons.

Neural projections

Processes extending from a neural cell, such as axons or dendrites, that are collectively called neurites.

Neuroendocrine neurons

Neurons that can release neurohormones following neuronal stimulation.

Neurogenic area

An area in the brain where neurogenesis, the process by which new neurons are formed, occurs.

Neurotrophic growth factors

Peptides primarily involved in the regulation of survival, growth and differentiation of neurons.

Neurotropism

Ability to invade or attract neural tissues.

Nociception

Perception or sensation of pain.

Noradrenergic neurons

Neurons that use norepinephrine (also known as noradrenaline) as a neurotransmitter.

Nucleus of the solitary tract

Group of sensory neurons that are located in the dorsomedial medulla of the brain.

Oligodendrocytes

Category of glial cells producing the myelin in the central nervous system.

Glossary (continued)

Orexinergic neurons

Neurons that release orexin, a peptide that regulates arousal, wakefulness and appetite.

Parabrachial nucleus

Area located in the dorsolateral pons of the brain and working as a sensory relay that receives visceral, nociceptive and thermoreceptive inputs from the periphery and transfers the information to the hypothalamus and amygdala.

Parasympathetic nerve fibres

Nerve fibres from the parasympathetic division of the autonomic nervous system, which is responsible for the rest and digestion response of the body.

Peptidergic

Describing neurons that secrete peptides as their neurotransmitters.

Phase shifts

Deregulation of circadian rhythms that originate in the suprachiasmatic nucleus of the brain, leading to a shift in the sleep or awake time.

Prefrontal cortex

PFC. Region of the brain that makes up the frontal area of the frontal lobe and is mainly involved in mediating complex cognitive processes.

Purinergic signalling

Extracellular signalling mediated by purine nucleotides and nucleosides such as adenosine or adenosine triphosphate (ATP).

Retinohypothalamic tract

Light-initiated signalling pathway that signals from the retina to the suprachiasmatic nuclei of the hypothalamus in the brain.

Schwann cells

Glial cells of the peripheral nervous system that help separate and insulate nerve cells.

Seed and soil theory

A hypothesis that states that metastatic tumour cells can only grow at a site with a favourable local tissue microenvironment, just like a seed will only grow if it lands on fertile soil.

Stereotactic activation

Electronically guided activation.

Substantia nigra

Brain region that is part of the basal ganglia and is involved in the production of the neurotransmitter dopamine.

Suprachiasmatic nucleus

SCN. Bilateral brain area located in the anterior part of the hypothalamus that is involved in the control of circadian rhythms.

Sympathectomy

Surgical procedure during which at least one sympathetic nerve or sympathetic ganglion is removed.

Sympathetic nervous system

Part of the autonomic nervous system that is best known for its role in responding to dangerous or stressful situations.

Sympatho-adrenal system

SAS. Physiological connection between the sympathetic nervous system and the adrenal medulla that regulates the release of catecholamines in response to environmental stimuli.

Thymic involution

Shrinking of the thymus that can occur naturally with age or acutely, as a consequence of stress, chemotherapy or other factors.

Tumour neo-angiogenesis

Formation of new blood vessels in the tumour microenvironment.

Viscero-sensory relays

Direct and indirect connections between sensory nerves of the autonomic nervous system and an organ.

cancer therapies. In addition, repurposing of neuropsychiatric drugs to achieve, for example, selective activation of central dopaminergic signalling pathways^{146–148} or the use of selective β-blockers to inhibit peripheral and central adrenergic nerve signalling can help to impair tumour development. In terms of patient well-being, mindfulness-based therapy, used as adjuvant cancer care, might also contribute to reducing distress and improve cognitive function in patients with cancer^{273–275}. Finally, immunohistochemical or molecular profiling of nerve fibres, neurons or neural cognate receptors might aid in stratifying patients whose tumours are more prone to responding to anti-neural therapies. Researchers are now beginning to appreciate the important role of the macro-neuro-environment and micro-neuro-environment in regulating cancer cell behaviour. Unravelling the peripheral and central nerve networks that drive tumour development in this new research area holds promise for the development of neuro-targeting cancer therapies.

We have herein presented and discussed evidence for the convergence of the central and peripheral nervous systems to sustain cancer development; however, many questions remain to be answered. Applying the principles of neuroscience to cancer biology and oncology is needed to bridge the gap and decipher the interplay between cancer and the nervous system, and discoveries in cancer neuroscience can, in turn, nurture the neuroscience field.

Moreover, the brain is the integration centre for cognition, emotions, social interactions and behaviour, and the recent developments

in cancer neuroscience that we have described here might also lead to further studies about neurophysiological, cognitive and psychosocial inputs in cancer. Cancer is already known to have a significant psychological impact²⁷⁶ and the bidirectional interactions between the tumour and the brain point to the need for further integrative studies. The potential relationships between cancer and psychology, psychosocial biology²⁷⁷ and psychiatry²⁷⁸ have already been highlighted but, with the exception of a few innovative studies, these research areas remain poorly connected to molecular oncology. Further efforts are warranted to unify these fields in a more holistic way. Molecular events occurring in cancer cells need to be integrated with molecular and functional events in the brain and interactions with the environment, including its social components. The remaining gaps between the fields of oncology, neuroscience, psychology, psychiatry and social sciences need to be surmounted in order to gain a more comprehensive and complete understanding of cancer and, ultimately, to care for patients with cancer as a whole.

Defining the role of multiple nerve signalling pathways in the brain or in the TME and elucidating their crosstalk and their respective influence on the initiation and progression of human cancer will provide new perspectives for a better understanding of the neural addiction of cancer and the complex cellular networks involved.

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Competing interests

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