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Tumour innervation as a regulatory layer of cancer immunity

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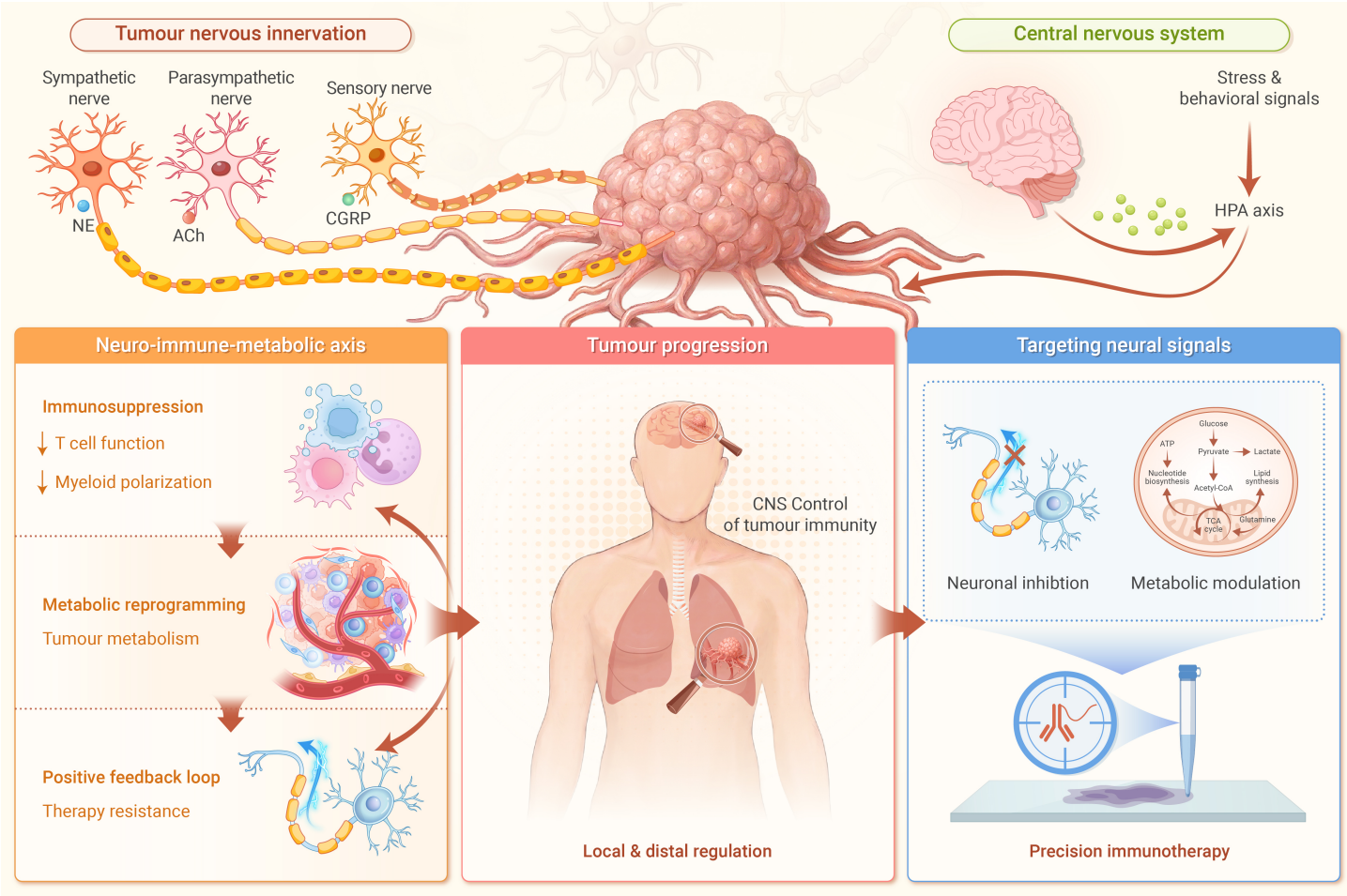
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Tumor innervation is a key regulator of the tumor microenvironment (TME) and affects cancer immunity.
- Neurotransmitters and neuropeptides shape immune cell function, forming a neuro–immune–metabolic axis.
- Neural signals interact with oncogenic pathways and exhibit marked heterogeneity within the TME.

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Tumour immune regulation has traditionally been interpreted through immune cell states, metabolic reprogramming, and genomic alterations. Although this framework has advanced cancer immunology, it does not fully explain the marked heterogeneity of the tumour immune microenvironment or the poor response of many immunologically "cold" tumours to immune checkpoint blockade. Emerging evidence identifies the nervous system as an important but underappreciated regulator of tumour immunity. Many solid tumours are densely innervated by sympathetic, parasympathetic, and sensory nerves, and increased neural fiber density is frequently associated with immunosuppression, tumour progression, and metastasis. Through predominantly non-synaptic signalling, neurotransmitters and neuropeptides modulate immune cell recruitment, T cell activity, myeloid polarization, and immune tolerance within the tumour microenvironment. Neural signals also reshape tumour metabolism, establishing a neuro–immune–metabolic axis that converts transient neural inputs into sustained immunosuppressive states and self-reinforcing feedback loops linked to therapeutic resistance. At the systemic level, the central nervous system further influences tumour immunity through stress-related neuroendocrine pathways and behavioral states. In this Review, we summarize current knowledge on tumour innervation, neuro–immune crosstalk, and their metabolic basis, and discuss how neural regulation may shape immunotherapy responses and offer new opportunities for precision immunomodulation in cancer.

THE NERVOUS SYSTEM AS AN OVERLOOKED REGULATORY LAYER OF TOMOUR IMMUNITY

Studies of tumour immune regulation have traditionally focused on three principal dimensions: immune cell functional states, tumour-intrinsic metabolic reprogramming, and genomic and epigenetic alterations.[1-5] Together, these processes shape the immunosuppressive tumour microenvironment (TME) and strongly influence clinical responses to immunotherapy. However, this framework alone does not fully explain the substantial heterogeneity of tumour immune landscapes across cancer types and individuals, nor does it adequately account for the limited efficacy of immune checkpoint inhibitors in immunologically "cold" tumours.[2,6-8]

Growing evidence now identifies the nervous system as a previously underappreciated but integral regulator of tumour immunity.[9,10] Many solid tumours are thought to be richly innervated, and several studies suggest that increased neural fiber density may be associated with tumour progression, immune suppression, and metastatic potential.[11-14] Through the release of neurotransmitters and neuropeptides, autonomic and sensory nerves directly influence tumour cells, stromal elements and immune populations, thereby shaping immune cell recruitment, effector activity and immune tolerance.[12,15-17] Unlike cytokine– or metabolism–driven signalling, neural communication is rapid, spatially precise and capable of integrating systemic physiological states, enabling tight coordination between local TME dynamics and whole–body immunity.[15,18-20] These observations support the concept that tumour immune states are not governed solely by immune, metabolic and genetic programs, but are continuously modulated by neuro–immune interactions.[21,22] Incorporating neural regulation into current models of tumour immunity offers a unifying framework to better understand immunosuppression and therapeutic resistance, and highlights new opportunities to convert immunologically cold tumours into immune-responsive disease.[23-26]

TOMOUR INNERVATION AND ROUTES OF NEURAL SIGNAL ENTRY INTO THE TME

Tumour innervation

A growing body of evidence shows that peripheral solid tumours are not devoid of neural influence but are innervated by sympathetic, parasympathetic and sensory nerves.[13,19,27] Neural inputs add a regulatory layer distinct from cytokine– and metabolite–based signalling: they transmit rapidly, operate with high spatial precision and are readily coupled to systemic stress responses, thereby linking local TME dynamics to whole-body immune states.[28-30] Clinical observations and experimental models suggest that increased neural fiber density may be linked to tumour progression, metastatic potential, and immunosuppressive phenotypes.[31-33] These findings suggest that tumour innervation is a structural contributor to heterogeneity within the tumour immune microenvironment (TIME).[34-36] Even among tumours with similar burden and mutational profiles, differences in neural input may constrain immune cell infiltration, promote T cell exhaustion and ultimately limit responsiveness to immunotherapy.[37-40] In this context, neural architecture emerges as a previously unrecognized determinant of immune competence within tumours.

Sources of neural input and signalling modalities

Tumour-associated neural networks arise through two main routes: incorporation of pre-existing peritumoural nerves and tumour-induced axonogenesis.[34,41,42] The latter mirrors angiogenesis and is commonly driven by tumour-derived neurotrophic factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which stimulate axonal growth and increase intratumoural neural density.[43-45] In addition to soluble cues, tumour–derived extracellular vesicles and exosomes can deliver axon guidance signals or reshape neuronal gene expression through microRNA-dependent mechanisms, further promoting neural remodeling and plasticity.[46-48]

Importantly, neural regulation within the TME extends beyond classical neuron-to-neuron communication.[49] Neurotransmitters and neuropeptides, as well as cholinergic and catecholaminergic signals, act in a paracrine manner on immune and stromal cells, forming a broad spectrum of non–synaptic signalling pathways.[50-55] Through these mechanisms, nerves function as integral structural components of the TME, providing both physical neural networks and sustained chemical inputs that continuously shape local immune niches.[56,57]

NEUROTRANSMITTERS DIRECTLY RESHAPE THE TOMOUR IMMUNE LANDSCAPE

Autonomic neurotransmitters and immunosuppression

Catecholamines released from sympathetic nerves, primarily noradrenaline and adrenaline, are increasingly recognized as important regulators

of immune activity within the TIME.[29,58,59] These neurotransmitters weaken anti-tumour immunity by reducing the effector function and persistence of $CD8^+$ T cells, promoting T cell exhaustion, and enhancing the expansion and suppressive activity of regulatory T cells (Tregs). Through these combined effects, sympathetic signalling limits immune-mediated tumour control.[60-64] Most of these immunomodulatory effects are mediated through signalling pathways centered on the β_2–adrenergic receptor (ADRB2).[64,65]

In $CD8^+$ T cells, activation of ADRB2 triggers the cAMP–PKA signalling pathway, which interferes with early T cell receptor (TCR) signalling by reducing phosphorylation of key components such as ZAP70 and ERK1/2. This effect limits early T cell activation and weakens cytotoxic T cell responses.[66-68] By contrast, in regulatory T cells the same pathway enhances transcription and stability of the lineage–defining factor FOXP3 through activation of STAT3 signalling, thereby promoting Treg expansion and reinforcing their immunosuppressive activity.[65] Adrenergic signalling also reshapes the myeloid compartment. In myeloid cells, catecholamines suppress nuclear translocation of NF-κB, leading to reduced production of pro–inflammatory cytokines such as TNF-α and IL-1β. At the same time, activation of the STAT6 pathway increases the release of anti-inflammatory mediators, including IL-10 and TGF-β. Together, these changes promote macrophage polarization toward an immunosuppressive phenotype, reduce antigen presentation, and dampen local inflammatory responses within the tumour microenvironment (Table S1) .[69-73]

Importantly, neural signalling does not function independently of tumour-intrinsic oncogenic pathways. Increasing evidence indicates that tumour genotype can shape neural signalling within the tumour microenvironment, creating points of interaction between oncogenic networks and neurotransmitter–driven pathways. Through this crosstalk, neural inputs and tumour–intrinsic signalling may jointly regulate key malignant traits and contribute to the dynamic remodeling of the tumour microenvironment.[48] In addition, sympathetic neural activity is closely linked to systemic physiological stress responses. Conditions such as pain, sleep disruption and psychological stress can therefore amplify adrenergic signalling and intensify its immunosuppressive effects.[58,74-78] This connection between systemic physiological states and local immune regulation provides a framework for understanding how host conditions influence tumour immunity, and may help explain the variability in immunotherapy responses observed among patients with the same tumour type.[74,79-83]

Sensory neuropeptides and immune regulation

Neuropeptides released from sensory nerves, particularly calcitonin gene–related peptide (CGRP) and substance P, play important roles in shaping tumour immunity and often exert highly localized effects within the tumour microenvironment.[84-88] Increasing evidence indicates that CGRP may promote exhaustion of tumour-infiltrating T cells by disrupting T cell receptor (TCR) signalling, which reduces the production of key effector cytokines, including interleukin-2 (IL-2) and interferon-γ (IFN–γ).[35,89-91] Mechanistically, CGRP binds to the RAMP1–CALCRL receptor complex on $CD8^+$ T cells and activates the Gαs–cAMP–PKA signalling pathway. This signalling cascade interferes with early TCR activation by suppressing phosphorylation of critical downstream molecules such as ZAP70 and ERK1/2, thereby limiting T cell activation and cytotoxic function.[92-94]

Beyond their direct effects on T cells, neural signals can promote immunosuppression by reshaping key immune signalling pathways in multiple immune cell types. Activation of the cAMP–PKA pathway influences central immune regulatory networks, including NF-κB and STAT6, through phosphorylation-dependent signalling and transcriptional regulation. These changes weaken antitumour immunity by promoting T cell exhaustion, impairing dendritic cell (DC) function and facilitating the expansion of Tregs and myeloid–derived suppressor cells (MDSCs). Together, these effects support the establishment of an immunosuppressive tumour microenvironment.[95,96] In addition, CGRP can further reinforce immune tolerance by impairing antigen presentation and altering myeloid cell function within the tumour microenvironment.[33,36,89,97,98]

Another sensory neuropeptide, substance P, signals primarily through the neurokinin-1 receptor (NK1R) and can regulate inflammatory transcriptional programs and immune checkpoint–related features in tumour cells.[89,99-102] Its effects may also interact with therapeutic interventions such as radiotherapy or neural–targeted treatments, leading to either synergistic or antagonistic outcomes.[103-105] Collectively, these observations suggest that neuropeptides act as upstream regulators of tumour immunity, operating partly independently of classical cytokine networks. Notably, neuropeptide signalling may precede overt immune phenotypic changes and is closely associated with tumour progression, metastatic dissemination and the development of cancer–associated pain.[106-110]

Context dependency

Neuro–immune interactions are strongly context dependent, and their effects vary with tumour type, anatomical location and stage of disease. The relative influence of sympathetic, parasympathetic and sensory neural pathways on immune regulation differs across cancers.[111] For example, in head and neck squamous cell carcinoma, sensory nerves promote the infiltration of granulocytic MDSCs and drive $CD8^+$ T cell exhaustion, partly through the release of small extracellular vesicles (sEVs). In contrast, in melanoma, sensory neurons primarily suppress antitumour immunity through CGRP–dependent signalling, which promotes $CD8^+$ T cell dysfunction and the accumulation of MDSCs.[112]

The effects of neural signals on tumour immunity can vary widely depending on the surrounding microenvironment.[111] For example, substance P can promote the production of IL-6 through activation of the neurokinin-1 receptor (NK1R), thereby strengthening immunosuppressive signalling. However, in certain breast cancer models with low baseline inflammation, inhibition of NK1R has been reported to increase metastatic risk. These contrasting outcomes likely reflect differences in the local immune milieu, including the baseline levels of inflammatory mediators within the tumour microenvironment.[113] In addition to signalling context, spatial organization also contributes to this heterogeneity. The physical proximity between neural fibers and immune cells can shape the strength and nature of neural influence on immune responses.[114] Together, these findings suggest that neural regulation of tumour immunity emerges from the integration of neural signal intensity, tissue architecture and cell-specific receptor expression.[115,116] From a translational perspective, this context dependency suggests that uniform neural modulation strategies are unlikely to be broadly effective.[117] Instead, therapeutic approaches may benefit from stratifying tumours according to their patterns of innervation and receptor expression, and targeting neuro–immune interactions within specific spatial niches of the tumour microenvironment (Figure 1).[118]

THE NEURO–IMMUNE–METABOLIC AXIS: NEURAL SIGNALS RESHAPE IMMUNE EFFECTOR FUNCTION THROUGH METABOLISM

Neural signalling drives immunometabolic reprogramming

Neural regulation of tumour immunity extends beyond direct effects on immune cell activation or suppression and is often mediated through changes in cellular metabolism that redefine immune effector capacity.[24,48,119,120] These interactions form a neuro–immune–metabolic axis in which brief neural inputs are translated into sustained immunosuppressive states, with important implications for therapeutic response.[121-123] Neurotransmitters and neuropeptides influence immune function not only through receptor signalling but also by altering energy availability and substrate use.[124-126]

During stress or heightened neural activity, sympathetic β-adrenergic signalling acts on both tumour and immune cells to promote metabolic adaptation.[127-129] tumour cells increase glycolysis and lactate production, leading to acidification of the tumour microenvironment and lactate accumulation.[130-132] This metabolic context impairs $CD8^+$ T cell migration, activation and cytotoxicity, and favors the development of exhausted T cell states, thereby weakening immune-mediated tumour control.[133,134] At the same time, neural signals reprogram myeloid Cell Metabolism by enhancing oxidative phosphorylation and fatty acid oxidation and activating lipid-associated immunosuppressive pathways, including prostaglandin E_2 production.[130,135,136] These changes support the differentiation and maintenance of tumour–associated macrophages and myeloid–derived suppressor cells.[78,79,137,138] Beyond enhancing their intrinsic metabolic activity, tumour cells can also induce mitochondrial transfer from neural stem cells through

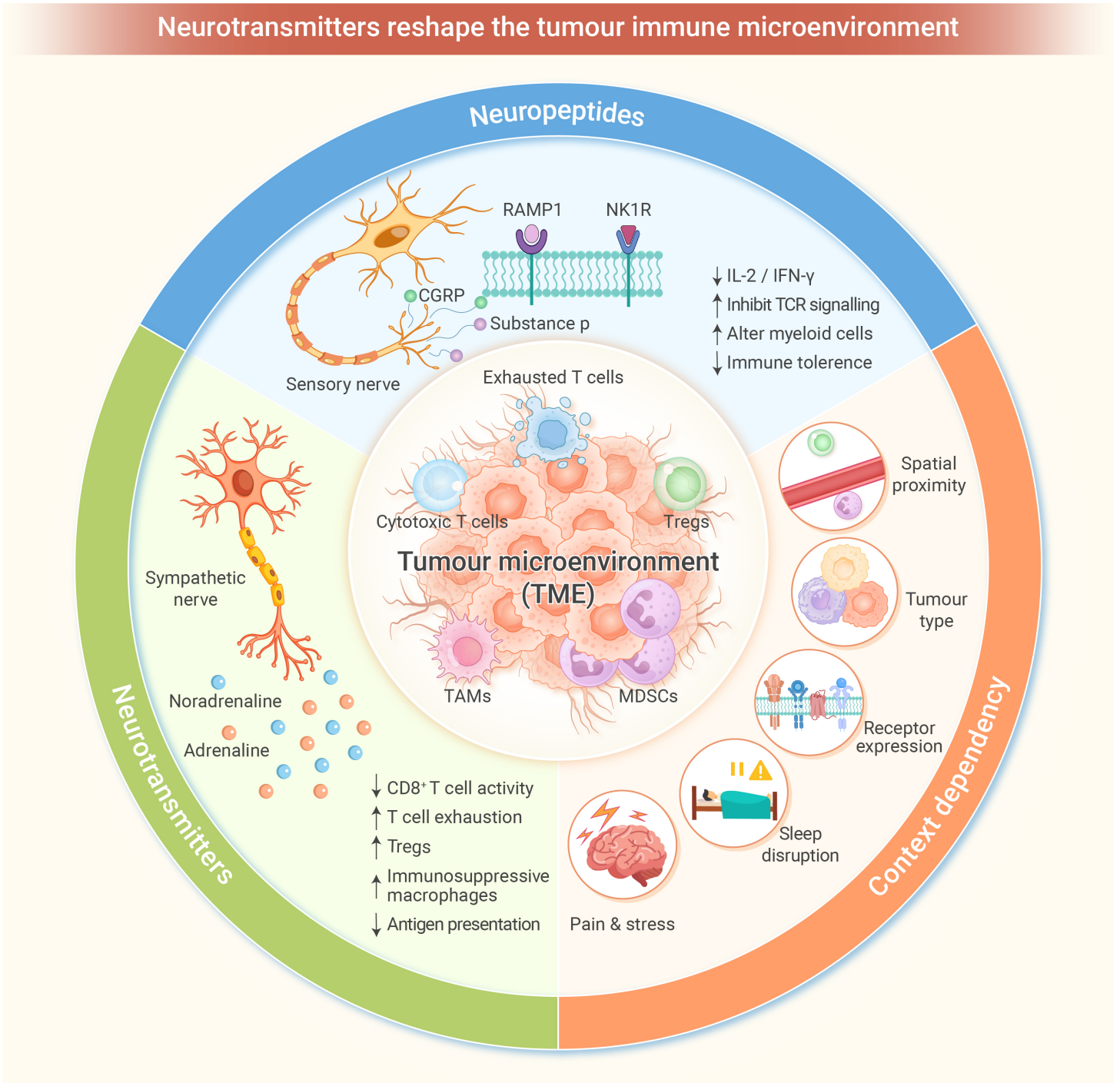

Figure 1. Neurotransmitters reshape the tumour immune landscape Neurotransmitters released from autonomic and sensory nerves directly influence the tumour immune microenvironment by suppressing $CD8^+$ T-cell activation, promoting T-cell exhaustion, and enhancing the expansion and suppressive activity of regulatory T cells and myeloid populations. Catecholamines from sympathetic nerves and sensory neuropeptides such as CGRP and substance P act through receptor-mediated signalling pathways, including ADRB2 and the RAMP1–CALCRL complex, to disrupt T-cell receptor signalling and modulate key immune regulatory networks such as cAMP–PKA, NF-κB, and STAT pathways. Through these mechanisms, neural signalling promotes a stable immunosuppressive tumour microenvironment that supports tumour progression and may contribute to variability in therapeutic responses.

tunnelling nanotubes (TNTs). This process increases the metabolic plasticity, stem–like properties and resistance to metastatic stress of cancer cells, thereby contributing to the remodeling of the tumour microenvironment.[139,140] Together, neural-driven metabolic reprogramming converts immunosuppression from a transient signalling outcome into a stable ecological property of the tumour microenvironment, reinforcing immune dysfunction and limiting the effectiveness of immunotherapy.

Metabolism amplifies neuro–immune interactions

Metabolic changes are not simply downstream effects of neural regulation but actively reinforce the strength and durability of neuro–immune interactions.[130,141,142] Metabolites generated by tumour and immune cells, including lactate, lipid-derived mediators and reactive oxygen species–associated signals, can amplify neural influence by reshaping local pH, nutrient availability and cellular stress thresholds.[143-146] These conditions heighten immune cell responsiveness to neurotransmitters and neuropeptides, thereby stabilizing immunosuppressive programs within the tumour microenvironment.[147]

Importantly, metabolic stress induced by therapy or nutrient limitation can further intensify this circuit.[148,149] Under such conditions, tumours may increase the expression of neurotrophic factors, promoting additional neural ingrowth and neuropeptide release[150-153]. The resulting positive feedback loop–enhanced neural input, reinforced metabolic adaptation and sustained

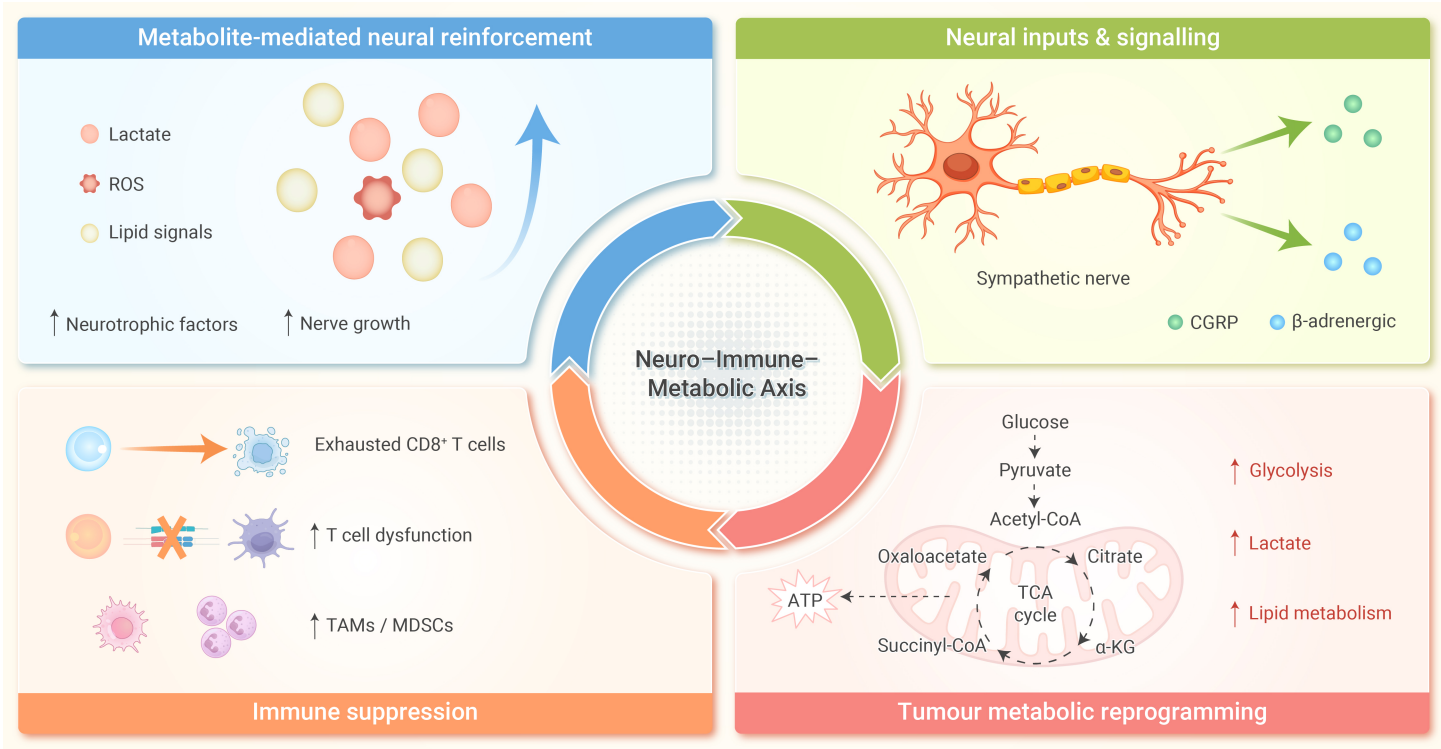

Figure 2. The neuro–immune–metabolic axis Neural signals reshape tumour metabolism by increasing glycolysis, lactate production, and lipid-associated metabolic pathways. These metabolic changes create a microenvironment that limits immune cell migration, activation, and cytotoxic activity. In turn, altered immunometabolic states promote the release of neurotrophic factors and other neural mediators, establishing a positive feedback loop that strengthens neuro–immune interactions and stabilizes an immunosuppressive tumour microenvironment.

immunosuppression–provides a mechanistic basis for the spatial and temporal heterogeneity of immunotherapy responses and for the development of therapeutic resistance (Figure 2).[34,47,110,154,155]

REMOTE IMMUNE REGULATION BY THE CENTRAL NERVOUS SYSTEM

The stress–immune–tumour axis

In addition to local neural inputs, the central nervous system (CNS) can remotely shape tumour immunity by translating systemic physiological states into immune programs through neuroendocrine pathways.[134,156-158] Chronic stress persistently activates sympathetic signalling and elevates catecholamine levels, while simultaneously increasing glucocorticoid release via the hypothalamic–pituitary–adrenal (HPA) axis.[159-161] Together, these pathways bias immune responses towards suppression by weakening T cell priming and effector function, promoting immunosuppressive myeloid and regulatory T cell programs, and, in certain contexts, impairing antigen presentation and tumour–specific immune initiation.[24,158,162-164] Consequently, immunosuppression is no longer restricted to the tumour site but becomes established as a systemic background state, shaping both the baseline immune context and the upper limit of responsiveness to immunotherapy.

Immunological consequences of behavior and neural states

Behavioral and neural states, including emotional stress, sleep patterns and pain, function as non-classical regulators of tumour immunity.[37,165-167] Sleep deprivation or circadian disruption is associated with altered immune cell trafficking, unstable effector function and reduced tumour surveillance.[168-170] Psychological stress and negative affective states further modify immune activation thresholds and inflammatory set points through neuroendocrine signalling.[171,172] Pain beyond serving as a clinical indicator of tumour innervation, may reflect sustained sensory nerve activation and is often accompanied by neuropeptide release and the formation of locally immunosuppressive niches.[16,173-175] Collectively, CNS–driven physiological and psychological states define the baseline conditions of the tumour immune microenvironment, thereby amplifying inter-patient variability in responses to otherwise identical therapeutic interventions (Figure 3).

THERAPEUTIC IMPLICATIONS AND FUTURE DIRECTIONS

Neural signalling as a modulator of immunotherapy

Incorporating neural regulation into immunotherapy offers new opportunities to address immune exclusion and treatment heterogeneity.[176-178] Preclinical and emerging clinical evidence indicates that β-adrenergic blockade can enhance responses to immune checkpoint inhibitors (ICIs) in selected tumour types and patient subsets, in part by increasing T cell infiltration, reducing suppressive myeloid populations and limiting T cell exhaustion.[179,180] However, these benefits are strongly context dependent, highlighting the need for patient stratification based on neural receptor expression, patterns of tumour innervation, stress–related physiology and baseline features of the tumour immune microenvironment.[181-183]

A representative example of biomarker-guided patient stratification involves the neural signalling receptor ADRB2. Studies show that ADRB2 can promote PD-L1 expression by upregulating the transcription factor SOX10, thereby contributing to tumour immune evasion.[184] In tumours with high ADRB2 expression, treatment with β-adrenergic blockers has been shown to activate $CD4^+$ T cell–mediated antimetastatic immunity. Importantly, this effect has been observed across multiple cancer types, supporting the ADRB2–SOX10–PD-L1 axis as a potential biomarker for patient stratification and as a therapeutic target for modulating neural–immune interactions in cancer.[185] Beyond adrenergic pathways, additional therapeutic opportunities may arise from targeting specific neuropeptide and neurotransmitter circuits, including CGRP, substance P, and cholinergic signalling. Modulating these pathways could complement existing treatments such as immune checkpoint inhibitors, radiotherapy, and metabolic therapies, offering new strategies to improve anti-tumour immune responses.[30,186,187] However, despite the promising therapeutic potential of targeting neural signalling pathways in cancer immunotherapy, their possible clinical risks must be carefully considered. Non-specific inhibition of adrenergic or neuropeptide signalling pathways may disrupt physiological neuro–immune interactions in normal tissues, potentially leading to immune dysregulation or dysfunction of the autonomic nervous system.[188,189] To mitigate these risks, recent studies have begun to explore more precise strategies, such as selectively targeting intratumoural nerve fiber regional neural circuits. These approaches aim to

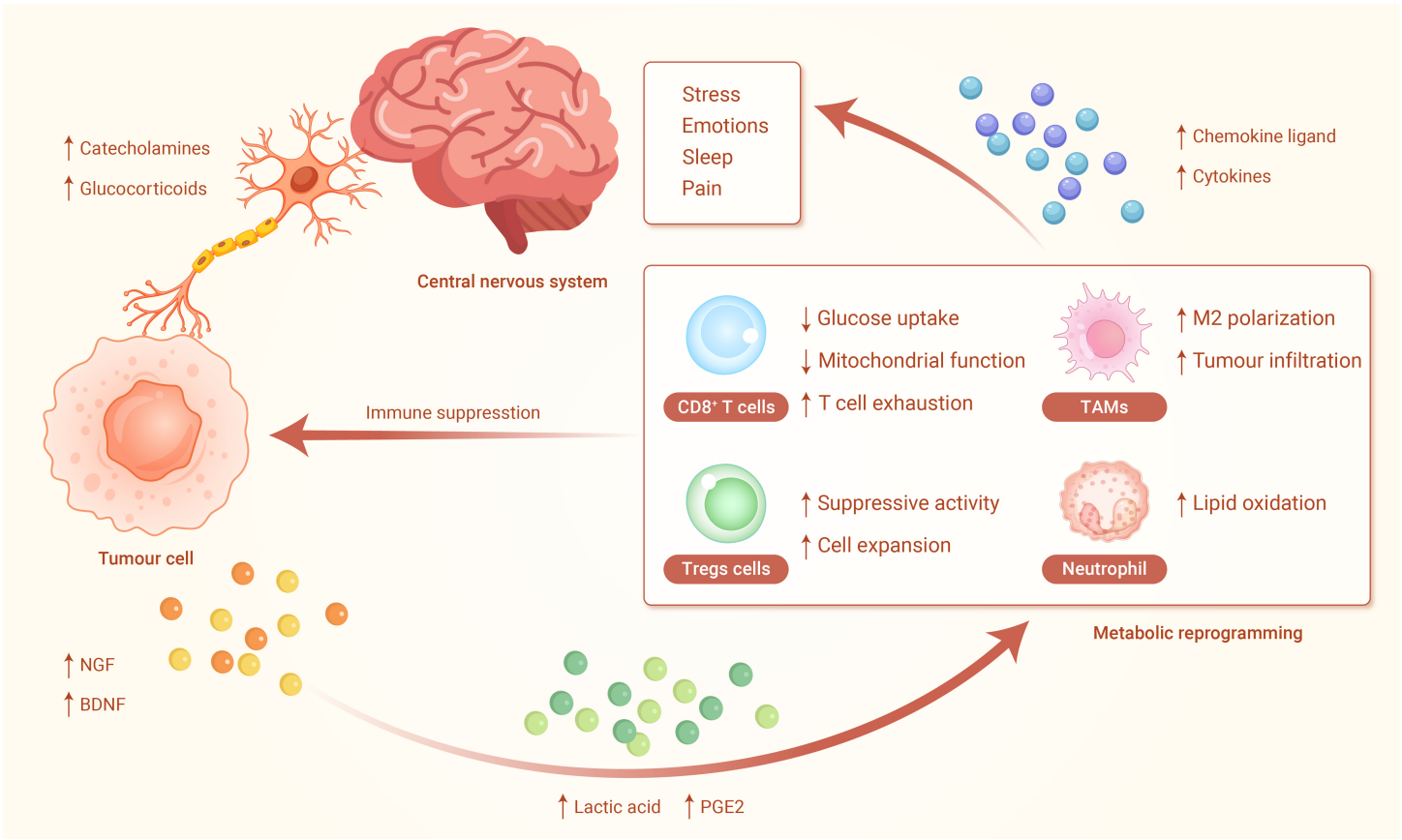

Figure 3. The neuro–endocrine–metabolic axis in tumour progression Physiological stressors such as chronic stress, sleep disturbance, and persistent pain activate sympathetic catecholamine signalling, glucocorticoid pathways, and β-adrenergic signalling. These neuroendocrine signals drive metabolic reprogramming in tumour cells, particularly increased glycolysis, which supports tumour growth, stem-like traits, and metastatic potential. At the same time, they reshape the tumour immune microenvironment by suppressing $CD8^+$ T-cell activity, promoting regulatory T-cell expansion, inducing immunosuppressive macrophage polarization, and impairing neutrophil function. Metabolic alterations further reinforce neural and immune interactions, forming a positive feedback loop that strengthens immunosuppression and promotes tumour progression.

specifically disrupt tumour-associated neuro–immune interactions while preserving normal neural–immune homeostasis, thereby reducing potential adverse effects (Table S2).[190]

Technological and methodological frontiers

Advancing neuro–immune oncology requires approaches that render neural signalling measurable, spatially resolved and experimentally controllable.[15,191,192] Spatial omics, integrated with neural tracing and tissue-clearing techniques, can map the spatial organization of neural fibers, immune cells and tumour cells at tissue scale.[193] Single–cell multi–omics and receptor–ligand analyses further enable definition of neural receptor landscapes and associated metabolic states across immune populations.[194,195] Complementing these descriptive tools, genetic, chemogenetic and optogenetic strategies allow causal manipulation of defined neural circuits or signalling pathways, supporting mechanistic links between neural inputs, metabolic reprogramming and immune outcomes.[196,197]

Open questions

Several key challenges remain. First, causality: it is still unclear when and where neural signals initiate immunosuppressive states within tumours, and whether these processes present reversible windows for therapeutic intervention. Second, tumour specificity: sympathetic, parasympathetic, and sensory pathways can produce distinct, and sometimes opposing, effects depending on cancer type, anatomical location, and disease stage. Third, clinical translation: identifying responsive patient populations, determining optimal treatment timing, and minimizing systemic side effects remain critical barriers. Addressing these questions will require reliable and stratifiable biomarkers. Potential indicators include neural fiber density within tumours, expression of neural receptors, as well as clinical features linked to neural activity, such as pain, sleep patterns, and stress-related hormone levels. Integrating these measures may help guide the precise targeting of neuro–immune interactions in cancer therapy.

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AUTHOR CONTRIBUTIONS

Study concept and design: W.D.N. and L.W.M. Draft of the manuscript: W.D.N., F.Z., Y.Z., L.H., L.Q.Y., and Z.D.X. Critical revision of the manuscript for important intellectual content: W.D.N. and L.W.M. Obtain funding: W.D.N. and L.W.M. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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