

Review Article

Psychological factors in tumor immunity: molecular mechanisms and therapeutic perspectives

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Received August 6, 2026; Accepted September 11, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: Immune checkpoint inhibitors (ICIs) have transformed cancer therapy. However, durable responses remain limited to a subset of patients. Accumulating evidence suggests that psychological factors, particularly chronic psychological stress (CPS), depression, and anxiety, may influence responses to immunotherapy. This review synthesizes recent evidence concerning three major pathways: the sympathetic nervous system-norepinephrine-beta-adrenergic receptor (SNS-NE- β -AR) axis, the hypothalamic-pituitary-adrenal-glucocorticoid (HPA-GC) axis, and vagus nerve-acetylcholine (VN-ACh) signaling. We summarize how catecholamines, glucocorticoids, and cholinergic mediators affect antitumor immunity. These mediators can promote effector T-cell dysfunction, recruit immunosuppressive myeloid cells, alter macrophage polarization, and regulate immune-checkpoint expression. They are also involved in tumor innervation and metabolic reprogramming. We further evaluate both pharmacological and non-pharmacological strategies targeting these pathways. Pharmacological approaches include β -blockers, inhibitors of glucocorticoid synthesis or metabolism, glucocorticoid-receptor antagonists, and cholinergic-receptor blockers. Nonpharmacological strategies include cognitive behavioral therapy, mindfulness-based stress reduction, environmental enrichment, and transcutaneous auricular vagus nerve stimulation. Although preclinical studies and retrospective clinical analyses provide a rationale for targeting these pathways, the available evidence is heterogeneous and requires confirmation in adequately powered prospective trials. Integrating psychological assessment with neuroendocrine and immune biomarkers may support risk stratification and the development of individualized combination strategies.

Keywords: Psychological factors, chronic psychological stress, tumor immunity, immune checkpoint inhibitors, neuroendocrine-immune network, beta-adrenergic receptors, glucocorticoids, vagus nerve

Introduction

Immune checkpoint inhibitors (ICIs), particularly antibodies targeting programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), have transformed the treatment of cancer. Nevertheless, substantial clinical challenges remain. Across multiple studies, only approximately 15%-30% of patients achieve durable clinical responses [1]. This marked interindividual variability has prompted investigation of host-related determinants of therapeutic response. Traditionally, differences in ICIs efficacy have been attributed primarily to

tumor-cell immune-evasion mechanisms, tumor mutational burden (TMB), and the composition and functional state of immune cells within the tumor microenvironment (TME). Increasing evidence, however, suggests that patients' psychological states may directly influence antitumor immunity through complex neuroendocrine-immune regulatory networks and may consequently modify clinical responses to immunotherapy.

Psychological factors, particularly chronic psychological stress (CPS), depressive symptoms or depressive disorders, and anxiety, have been

associated with cancer development, progression, and prognosis. These associations have made psychological factors an increasingly important focus of oncological research. By modifying the systemic physiological milieu through neuroendocrine-immune regulation, psychological states may contribute to heterogeneity in immunotherapeutic responses and may reveal potential intervention targets. This concept has received preliminary support from prospective clinical studies and experimental models, and accumulating evidence suggests that psychological assessment may have value in comprehensive cancer care [1-3]. A prospective study of patients with non-small cell lung cancer (NSCLC) receiving ICIs introduced the concept of a “psychobiomarker” and proposed incorporating emotional distress (ED) into routine assessment to identify high-risk patients who may benefit from early intervention [1].

Persistent ED has been associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), accompanied by increased release of stress mediators, including glucocorticoids (GCs), epinephrine, and norepinephrine (NE), and downstream alterations in immune function [4, 5]. Many immune-cell populations that infiltrate tumors express adrenergic receptors and are regulated by adrenergic signaling [6-9]. placebo-controlled, crossover trials with beta blocker drugs and a phosphodiesterase inhibitor during steady-state and graded exercise, and a synthetic β agonist (isoproterenol). Catecholamines predominantly act through β -adrenergic receptors (β -ARs) expressed by immune cells and other cellular components of the tumor microenvironment, thereby reshaping cytokine and chemokine networks, promoting the expression of immunosuppressive molecules and T-cell exhaustion, and ultimately impairing effector T-cell infiltration, proliferation, and cytotoxicity. These effects facilitate tumor immune escape and may reduce the efficacy of ICIs [10-15]. Epinephrine has also been reported to promote tumor vascularization and stem-like properties [16, 17]. Pre-clinical and clinical observations further suggest that glucocorticoid-receptor antagonists and β -blockers may improve responses to ICIs in selected settings [2, 18]. Psychological manifestations such as depression and anorexia

have also been associated with tumor-inflammation-induced dysfunction of the vagal brain-liver axis, which may promote cancer cachexia and compromise immunotherapeutic efficacy [19].

Despite these advances, a central question remains: how are psychological factors translated into altered antitumor immunity through neuroendocrine pathways? Understanding the underlying molecular and cellular mechanisms may also reveal potential targets for therapeutic intervention. This review therefore focuses on the SNS-NE- β -AR, HPA-GC, and vagus nerve (VN)-acetylcholine (ACh) pathways, which represent major neuroendocrine routes linking psychological states to the tumor immune microenvironment. We further evaluate potential pharmacological and nonpharmacological strategies targeting these pathways and discuss their translational potential and current limitations.

An integrated neuroimmune framework

Within the TME of solid tumors, the SNS-NE- β -AR, HPA-GC, and VN-ACh pathways, together with tumor-infiltrating nerves, may remodel immune, metabolic, stromal, and vascular compartments through interconnected molecular mechanisms. Negative psychological states, including chronic anxiety and depression, are processed within central regions such as the basolateral amygdala (BLA), hippocampus, and medial prefrontal cortex (mPFC), which can initiate neuroendocrine-immune signals that reach peripheral tumors [20, 21]. Hyperactive amygdala-related circuits may influence the hypothalamic paraventricular nucleus (PVN) through relay structures including the central amygdala (CeA), medial amygdala (MeA), and bed nucleus of the stria terminalis (BNST), thereby promoting corticotropin-releasing hormone (CRH) secretion and initiating the HPA cascade. In parallel, hypothalamic and brainstem nodes, including the PVN, rostral ventrolateral medulla (RVLM), and nucleus tractus solitarius (NTS), coordinate sympathetic output, vagal afferent integration, and autonomic balance [22-26] (**Figure 1**).

Key neural mediators and cellular targets

Sympathetic activation increases catecholamine release, predominantly NE, and stimulates

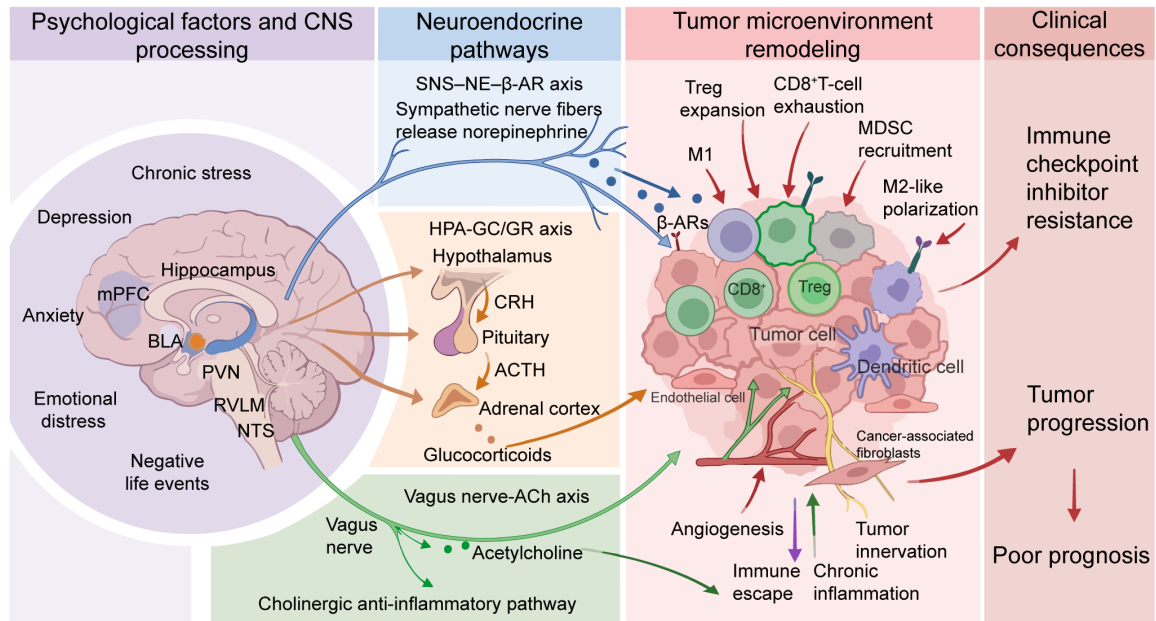


Figure 1. Neuroendocrine-immune mechanisms linking psychological factors to tumor immunity and immunotherapy response. Negative psychological factors engage sympathetic adrenergic, HPA-GC/GR, and vagal/cholinergic pathways, which remodel immune, stromal, vascular, and metabolic components of the tumor microenvironment and may promote immune escape, ICI resistance, tumor progression, and poor prognosis. Vagal effects are context dependent, differing between systemic vagal regulation and tumor-local cholinergic signaling. For clarity, the neural structures shown in Figure can be broadly grouped into limbic regions involved in emotional appraisal (e.g., BLA, hippocampus, and mPFC), hypothalamic nodes coordinating endocrine output (particularly the PVN), and brainstem regions integrating autonomic signals (including the NTS and RVLM). Figure illustrates representative neural nodes and their connections with peripheral neuroendocrine pathways. Colors indicate sympathetic adrenergic (blue), HPA-GC/GR (orange), systemic vagal (green), tumor-local cholinergic (purple), and downstream consequences (red).

β -ARs on tumor and immune cells. Within the TME, this pathway has been reported to promote angiogenesis, stromal remodeling, invasion, and metastasis while inducing immunosuppressive responses, including impaired $CD8^+$ T-cell function and differentiation, polarization toward M2-like macrophages, and recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [13, 27-29]. Infiltrating sympathetic fibers can further increase local NE concentrations, enabling SNS signaling to act not only through systemic stress responses but also through direct local innervation of the tumor [30].

GCs released through HPA-axis activation exert pleiotropic effects in the TME through the glucocorticoid receptor (GR). Tumor cells and stromal cells may express enzymes such as 11β -hydroxysteroid dehydrogenase type 1 (11β -HSD1), which converts inactive GC metabolites into active hormones and thereby amplifies local GC signaling [31]. Activated GR signaling enhances the suppressive activity of $CD4^+$

Tregs while impairing the effector and cytotoxic functions of $CD8^+$ T cells, thereby facilitating immune escape [32]. The SNS and HPA axis do not operate independently; stress commonly activates both pathways, producing coordinated increases in NE and GCs and establishing overlapping protumor and immunosuppressive signals within the TME.

VN-ACh signaling has context-dependent effects within the TME. In some tumor types, ACh may exert anti-inflammatory or immunostimulatory effects; in others, vagally derived or tumor-derived ACh acts through nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs) on immune, stromal, or vascular cells to alter the immune microenvironment [33-36]. Thus, VN signaling may counterbalance the protumor effects of the SNS or HPA axis under some conditions, whereas vagal stimulation may promote tumor progression in specific cancer types [37, 38].

Intratumoral sympathetic, parasympathetic, and sensory fibers provide a local neural interface through which these pathways act within the TME. Tumors can secrete neurotrophic factors, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), to promote neurite outgrowth and axonogenesis, thereby strengthening direct nerve-tumor interactions [39]. Neurotransmitters and neuropeptides released from these fibers act on tumor cells, immune cells, endothelial cells, and fibroblasts, reinforcing SNS, HPA, and VN signaling. Neural input may also induce metabolic reprogramming, including enhanced glycolysis and altered lipid metabolism, to support tumor-cell energetics and immunosuppression [40, 41].

The SNS-NE- β -AR axis and related therapeutic strategies

Sympathetic catecholaminergic signaling links psychological states to antitumor immunity. SNS activation releases norepinephrine and epinephrine, which bind adrenergic receptors on tumor and immune cells. These signals alter immune-cell activation, migration, and effector function, thereby reshaping the tumor immune landscape.

Negative affect, norepinephrine, and β 1-adrenergic receptor signaling in tumor immunosuppression

Increased catecholamine release during chronic stress can promote CD8⁺ T-cell exhaustion through β 1-adrenergic receptor (β 1-AR; encoded by ADRB1) signaling in chronic infection and tumors. In mouse models, genetic deletion of ADRB1 or pharmacological blockade of β 1-AR limits differentiation toward terminal exhaustion and enhances immune responses when combined with ICIs [13]. Collectively, these preclinical findings provide a mechanistic rationale for evaluating sympathetic-catecholaminergic signaling as a therapeutic target in immuno-oncology.

In an exploratory analysis of the European Organisation for Research and Treatment of Cancer (EORTC) 1325/KEYNOTE-054 study, patients receiving pembrolizumab together with a β 1-selective blocker had a 3-year progression-free survival (PFS) rate of 76.1%, compared with 62.5% among those not receiving a β 1-selective blocker [42]. This observa-

tion is compatible with the proposed immunomodulatory effect of β 1-AR blockade; however, the exploratory association cannot establish causality and requires confirmation in prospective, appropriately controlled studies.

In stress-exposed melanoma models, treatment of Me18105 and C8161 cells with 10 μ M NE for 6 h increased vascular endothelial growth factor (VEGF) expression to 1.95-fold that of controls ($P < 0.001$), increased interleukin-6 (IL-6) protein by more than 30-fold, and increased interleukin-8 (IL-8) by 3.2-fold [43]. These findings suggest that NE can directly enhance proangiogenic, chemotactic, and autocrine signaling in tumor cells, thereby creating conditions that may favor inflammation-associated immune suppression.

NE also enhances the suppressive activity of MDSCs by increasing arginase 1 and inducible nitric oxide synthase (iNOS). It can also upregulate melanoma-cell PD-L1 through the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) pathway [44]. Catecholamines may additionally promote M1-to-M2-like macrophage polarization and interleukin-10 (IL-10) production, whereas adrenergic blockade can restore selected leukocyte functions and enhance antitumor immunity [45]. Collectively, these effects can reduce CD8⁺ T-cell activity, increase infiltration by suppressive myeloid cells, and enhance tumor immune escape.

Consistent with this mechanism, Globig et al. evaluated atenolol alone or in combination with immune checkpoint blockade (anti-PD-1 plus anti-CTLA-4) in the YUMMER1.7 melanoma model. Compared with untreated tumors or those treated with atenolol alone, tumors receiving the combination therapy were significantly smaller, and this antitumor effect was dependent on CD8⁺ T cells [13]. This preclinical evidence supports further evaluation of β 1-AR blockade in combination with ICIs, while its efficacy and safety in patients remain to be established [13, 14, 46].

β 2-adrenergic receptor signaling in tumor progression and treatment resistance

The β 2-adrenergic receptor (β 2-AR; encoded by ADRB2) is an important mediator of cancer-related effects during chronic stress. SNS-derived NE binds β 2-AR on tumor cells and can

suppress the RNA demethylase ALKB homolog 5 (ALKBH5), leading to altered N6-methyladenosine (m6A) modification and increased tumor innervation [47]. Elevated catecholamines may also stimulate NGF and BDNF secretion and promote tropomyosin receptor kinase (Trk)-dependent axonogenesis, thereby increasing adrenergic innervation of the TME [48]. These findings suggest that SNS activation can influence tumor biology through both epigenetic regulation and neural remodeling.

In KrasG12D/+; Trp53R172H/+; Pdx1-Cre (KPC) mice, ICIs alone did not substantially reduce tumor size, whereas combining ICI treatment with 6-hydroxydopamine (6-OHDA)-mediated denervation produced an approximately 5.7-fold reduction in tumor volume [49]. β -Blockade of ADRB2 signaling and/or pharmacological inhibition of Trk receptors also reduced stress-induced neural infiltration of pancreatic tumors and delayed tumorigenesis [48]. These observations provide a preclinical rationale for combined targeting of ADRB2 and neurotrophin signaling, but their preventive or therapeutic value in high-risk populations remains unproven.

Depressive-like states may further promote cancer progression through SNS activation. In prostate cancer models, β 2-AR activation increases neuropeptide Y (NPY) release, which recruits and activates myeloid cells and establishes an IL-6-high inflammatory microenvironment [50]. β -Adrenergic signaling can also impair DNA-damage repair and p53-dependent apoptosis through mechanisms involving ataxia telangiectasia and Rad3-related kinase (ATR)-p21 signaling and AKT-dependent activation of the E3 ubiquitin ligase mouse double minute 2 homolog (MDM2), which promotes p53 degradation [51-54]. The nonselective β -blocker propranolol can increase p53 abundance, enhance tumor-cell apoptosis, and increase sensitivity to the topoisomerase I inhibitor SN-38 [51].

During chronic stress, NE-mediated activation of the β 2-AR-cAMP-PKA-cAMP response element-binding protein (CREB) pathway can increase transcription of circadian locomotor output cycles kaput (CLOCK) and induce stem-like tumor phenotypes [55]. In experimental lung cancer, olanzapine-mediated inhibition of the mPFC-NE-CLOCK axis reversed stress-

associated stem-like features and chemoresistance [55]. These observations provide a rationale for evaluating NE- β 2-AR signaling and its downstream pathways as adjunctive targets in tumors associated with persistent psychological distress or treatment resistance; prospective clinical validation is required.

β 3-adrenergic receptor signaling and its potential therapeutic relevance

Although β 1-AR and β 2-AR signaling have been extensively investigated, the regulatory mechanisms and clinical relevance of β 3-adrenergic receptor (β 3-AR) in cancer remain less well characterized. Catecholamine-induced β 3-AR activation has been implicated in tumor-cell proliferation and invasion, whereas β 3-AR antagonism may counter these effects by targeting downstream pathways [13, 15, 56]. In neuroblastoma, β 3-AR blockade has been reported to regulate the sphingosine kinase 2 (SK2)/sphingosine-1-phosphate receptor 2 (S1P2) pathway, reduce proliferation, and promote neuronal differentiation [56]. This pathway may provide a differentiation-based target in high-risk neuroblastoma, although clinical validation is lacking.

β 3-AR antagonism has also been reported to modulate interferon- γ (IFN- γ) production by tumor-infiltrating lymphocytes (TILs) and reduce PD-L1 expression on tumor cells [15]. However, because IFN- γ can exert both antitumor and adaptive immune-resistance effects, the net consequence of this pathway requires careful clarification. Most available evidence is preclinical, and the generalizability of β 3-AR targeting across tumor types remains uncertain. Future studies should define tumor-specific mechanisms, pharmacological selectivity, and biomarkers of response before β 3-AR can be considered a clinically actionable target.

Environmental enrichment and the SNS- β -AR axis

Most research has focused on adverse stressors and negative affect, whereas the effects of beneficial environmental stimulation on cancer biology remain incompletely understood. Under environmental enrichment (EE), SNS- β -AR signaling may not uniformly promote tumor progression. Instead, it has been reported to suppress C-C motif chemokine ligand 2 (CCL2)-

dependent myeloid-cell recruitment, increase CD8⁺ T-cell infiltration, remodel the TME toward an antitumor state, and enhance the efficacy of ICIs [13]. These context-dependent effects may reflect differences in catecholamine concentration, temporal signaling, and tissue-specific distribution of β -AR subtypes. Thus, the biological consequences of SNS activation depend not only on signal intensity but also on the nature of the environmental stimulus.

These mechanistic observations have stimulated interest in pharmacological blockade of the SNS-NE- β -AR axis as a strategy to relieve immune suppression and improve ICI efficacy. β -Blockers are widely used cardiovascular drugs with well-characterized safety profiles, and the nonselective agent propranolol has received particular attention. Several observational studies have associated concomitant β -blocker use with longer overall survival (OS) and PFS among patients receiving ICIs [57, 58]. However, clinical findings are heterogeneous, and some retrospective studies have identified benefits only in particular tumor types or with specific β -blockers [59, 60]. Potential explanations include confounding by indication, differences in dose and drug selectivity, timing of exposure, and patient selection.

An early-phase clinical study evaluated propranolol in combination with pembrolizumab for advanced melanoma [61]. Preliminary findings suggested acceptable tolerability and potential antitumor activity. Although mature comparative evidence is still needed, this study illustrates the transition from mechanistic and observational evidence toward prospective evaluation of SNS- β -AR modulation as an adjunct to immunotherapy.

The HPA-GC axis and intervention strategies

The HPA axis is a major interface between psychological processes and peripheral immunity. In response to persistent psychological stress, such as social defeat or chronic unpredictable stress, or to disruption of physiological homeostasis, the PVN releases CRH, which stimulates the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH). ACTH then drives adrenal-cortical synthesis and systemic release of GCs [62, 63]. Although GCs are essential for physiological homeostasis, metabolism, and immune regulation, persistent HPA-axis activa-

tion in patients with cancer may elevate GC concentrations in the circulation and tumor tissue and thereby reprogram tumor-infiltrating immune cells through broadly expressed GR [2].

GCs act through GR, which translocates to the nucleus and regulates the transcription of thousands of genes [62]. Tumors may also amplify GC signaling independently of de novo adrenal synthesis. In particular, 11 β -HSD1 converts inactive circulating GC metabolites into active hormones, increasing local GC exposure within the TME [31]. This local regeneration can enhance Treg activity and suppress CD8⁺ T-cell effector function, producing a strongly immunosuppressive environment [32, 64]. Recent work in mouse models of colorectal cancer and melanoma showed that chronic stress induces intratumoral GC production by cancer-associated fibroblasts through a microbiota-dependent mechanism, thereby impairing antigen-specific germinal-center B-cell responses [65].

Persistent HPA-axis activation during chronic stress or depression has been proposed to impair immune responses and contribute to the development or progression of selected cancers [66]. In an animal study examining stress duration, prolonged exposure reduced the abundance or activity of myeloid and lymphoid cells, bone-marrow stem cells, circulating immunoglobulins, and interleukin-12 (IL-12) [64]. Depression-associated elevations in GCs have also been linked to reduced CD4⁺ and CD8⁺ T-cell numbers, increased B-cell abundance, and altered cytokine profiles, including higher IFN- γ and interleukin-1 β (IL-1 β) and lower interleukin-2 (IL-2) and IL-10 [67-70]. These changes may reduce responsiveness to anti-PD-L1 therapy.

Dysregulated HPA signaling may also weaken anti-inflammatory feedback and sustain production of inflammatory mediators, including IL-1 β , IL-6, tumor necrosis factor alpha (TNF- α), and C-reactive protein (CRP) [71, 72]. These observations illustrate that prolonged GC exposure can produce both immunosuppressive and dysregulated inflammatory states, depending on cell type, dose, timing, and tissue context.

GC signaling profoundly influences T-cell differentiation and function. GR expression increases as CD8⁺ TILs progress from a naive or progenitor-like state toward dysfunction [73]. At the transcriptional level, GR cooperates with runt-related transcription factor (RUNX)-family factors, and GR-bound regions are enriched for RUNX motifs. This program is associated with increased expression of inhibitory receptors, including PD-1, lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin and mucin-domain containing 3 (TIM-3), and CTLA-4, thereby promoting CD8⁺ T-cell exhaustion [73, 74].

GCs also disrupt T-cell metabolism. By reducing glycolytic flux in CD8⁺ T cells, GC signaling can constrain antitumor activity even when inhibitory-receptor signaling is blocked [31, 75]. In addition to suppressing effector T cells, GCs enhance Treg function [32, 76]. Stress-induced systemic GC elevation can increase C-X-C chemokine receptor 4 (CXCR4) expression in the bone marrow, mobilize MDSCs, and suppress the proliferation and cytotoxicity of CD8⁺ T cells [77].

GCs can induce miR-342-3p in Tregs, which directly targets RICTOR, a core component of mechanistic target of rapamycin complex 2 (mTORC2), and activates a suppressive Treg program [76]. Treg-specific deletion of GR delays tumor growth and restores CD8⁺ T-cell activity in experimental models [31]. HPA-mediated immunosuppression also extends beyond transcriptional regulation: stress-induced GC signaling increases the catalytic activity of circulating dipeptidyl peptidase 4 (DPP4), promotes myeloid-cell expansion, and inhibits T-cell activation [78].

Although physiological GC release has potent anti-inflammatory effects, excessive or prolonged GC exposure can suppress immunity by inducing apoptosis or dysfunction in T cells, neutrophils, and antigen-presenting cells [79]. For example, stress-associated increases in plasma cortisol correlate with expression of TSC22 domain family member 3 (TSC22D3) in dendritic cells. Increased TSC22D3 suppresses type I interferon signaling and activation of IFN- γ ⁺ T cells, thereby reducing responses to immunogenic chemotherapy, including oxaliplatin and mitoxantrone, as well as PD-1 blockade and tumor vaccination [2].

Clinical data from patients with lung cancer have shown positive associations among plasma cortisol, TSC22D3 expression in peripheral leukocytes, and negative-affect scores [2]. These observations provide a rationale for investigating stress-associated GC signaling as a therapeutic target. Pharmacological inhibition of 11 β -HSD1 has reduced tumor growth and improved responses to anti-PD-1 therapy in experimental models [32, 80]. The selective 11 β -HSD1 inhibitor J2H-1702 has also been reported to reverse endothelial-to-mesenchymal transition (EndMT) and modulate M2-like macrophage polarization in multicellular lung spheroids containing lung-cancer cells, endothelial cells, and macrophages [81].

The GR antagonist mifepristone reversed the adverse effect of social-defeat stress on chemotherapy in mouse models [2]. By contrast, metyrapone is an inhibitor of adrenal steroidogenesis rather than a GR antagonist and has been reported to partially restore immune homeostasis and anti-PD-L1 responsiveness in depression-related experimental settings [67]. Nonpharmacological approaches, including cognitive behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR), may lower perceived stress and provide an upstream means of modulating HPA activity [68, 82, 83].

VN-ACh signaling and therapeutic intervention

The vagus nerve exerts many of its physiological effects through release of the neurotransmitter ACh [84]. Its role in tumor immunity is bidirectional. Systemically, vagal signaling can limit excessive inflammation through the cholinergic anti-inflammatory pathway (CAP); locally, however, cholinergic signaling may be co-opted by tumor cells to promote immune escape [37, 84]. Depression and anxiety are associated with reduced heart rate variability (HRV), suggesting impaired vagal regulation [85, 86].

The anti-inflammatory effect of vagal signaling depends on an intact CAP, which regulates macrophage activation and suppresses release of mediators such as TNF- α [87]. Chronic anxiety and depression are associated with reduced vagal tone and may weaken this inhibitory pathway [88]. Reduced vagal regulation can permit persistent systemic increases in IL-6, TNF- α , and other inflammatory mediators

[89, 90]. Such chronic low-grade inflammation may support tumor progression, impair T-cell metabolic fitness, and reduce the efficacy of ICIs, potentially contributing to an immunologically “cold” TME [19, 90].

Tumor-associated systemic inflammation may in turn impair vagal function. Increased CCL2 has been linked to neuroinflammation in the dorsal motor nucleus of the vagus and abnormal vagal reflexes [19]. Through the brain-liver axis, these signals can cause depletion of hepatocyte nuclear factor 4 alpha (HNF4 α), a central regulator of hepatic metabolism [19, 91]. Loss of HNF4 α promotes systemic metabolic reorganization, muscle wasting, adipose-tissue loss, and depressive-like behavior. These findings suggest a potential positive-feedback loop linking psychological distress, neuroimmune dysregulation, cachexia, and tumor progression.

Local ACh signaling may suppress antitumor immunity in selected tumors [88, 89]. Psychological stress has been reported to increase ACh signaling and expression of the $\alpha 5$ nicotinic acetylcholine receptor ($\alpha 5$ -nAChR), thereby promoting invasion and migration of lung-adenocarcinoma cells [92, 93]. In colorectal-cancer and melanoma models, increased ACh-nAChR signaling induces PD-L1 expression and may reduce sensitivity to ICIs [94, 95]. Tumor cells can also produce ACh in an autocrine manner, activating cholinergic receptors to support proliferation, migration, and immune escape [93].

ACh can directly inhibit effector T cells. Binding of ACh to the M3 muscarinic acetylcholine receptor (CHRM3) on CD8 $^{+}$ T cells suppresses IFN- γ production and release of cytotoxic granules, weakening tumor immune surveillance [96]. In preclinical models of liver cancer, hepatic vagotomy or pharmacological CHRM3 blockade interrupted cholinergic immunosuppression and restored T-cell antitumor activity [96, 97]. These findings support peripheral autonomic signaling as a potential target for combination therapy, although the safety, reversibility, and tumor specificity of denervation strategies require careful evaluation.

The vagal brain-liver axis also contributes to cancer-associated cachexia, and experimental interruption of this pathway can attenuate sys-

temic metabolic dysfunction [19, 91]. Nevertheless, vagal signaling is physiologically widespread and context dependent. Therapeutic modulation should therefore aim to preserve beneficial anti-inflammatory functions while preventing tumor-promoting cholinergic signaling [88, 90, 96, 97].

Clinical translation of vagal-pathway research has focused on biomarkers and combination strategies. HRV is a noninvasive marker of autonomic balance and psychological stress; low baseline HRV has been associated with poor prognosis in patients with cancer and has been proposed as a candidate stratification marker for autonomic interventions [98-100]. Physical and psychological approaches, including MBSR and transcutaneous auricular vagus nerve stimulation (taVNS), may modulate neuroimmune networks. In preclinical work, taVNS increased intratumoral CD8 $^{+}$ T-cell density and IFN- γ expression [101]. However, evidence that MBSR consistently improves HRV is limited by heterogeneity in study design and populations, and immune activation induced by neural stimulation does not necessarily translate into tumor control [101, 102].

Pharmacological CHRM3 blockade represents another investigational strategy. Agents such as solifenacin and darifenacin may reduce PD-L1 expression driven by the epidermal growth factor receptor/phosphorylated extracellular signal-regulated kinase (EGFR/p-ERK) pathway and may cooperate with PD-1 blockade [94-96]. Repurposing established drugs to target neuroimmune signaling warrants further investigation, but prospective studies are needed to determine tumor specificity, safety, dosing, and clinical efficacy.

Intervention strategies and clinical translation

Because neuroendocrine-immune interactions have emerged as potential regulators of the TME, current translational research is exploring pharmacological and nonpharmacological interventions that may mitigate treatment resistance associated with psychological distress and improve the effectiveness of existing immunotherapies (Table 1).

Targeting the SNS-NE- β -AR axis

Interventions targeting the SNS axis are among the most intensively investigated transla-

Psychological factors and tumor immunity

Table 1. Neuroendocrine and neural pathways linking psychological factors to tumor immunity and responses to immune checkpoint inhibitors

Pathway or neural component	Principal mediators, receptors, and signaling components	Major effects on the tumor microenvironment	Potential implications for ICI response	Candidate interventions
SNS-NE- β -AR axis	Norepinephrine; epinephrine; β 1-AR, β 2-AR and β 3-AR; cAMP-PKA-CREB.	CD8 ⁺ T-cell dysfunction and exhaustion; reduced IFN- γ and TNF; MDSC recruitment and enhanced suppressive activity; M2-like macrophage polarization; PD-L1 upregulation; angiogenesis; stress-associated tumor innervation; Environmental enrichment may exert context-dependent antitumor effects in preclinical models.	May promote immune escape and reduce sensitivity to PD-1/PD-L1 blockade; clinical evidence for β -blockade remains heterogeneous.	β -blockers, including propranolol and atenolol; selective β -AR blockade; Trk inhibition; experimental denervation; combination with ICIs.
HPA-GC/GR axis	CRH; ACTH; cortisol and other glucocorticoids; GR; 11 β -HSD1; RUNX; CXCR4; TSC22D3; DPP4.	Enhanced Treg suppressive activity; MDSC mobilization; CD8 ⁺ T-cell dysfunction; reduced glycolysis and cytotoxicity; impaired dendritic-cell type I IFN signaling and T-cell activation.	May promote immune escape and contribute to resistance to ICIs.	GR antagonism (mifepristone); glucocorticoid synthesis inhibition (metyrapone); 11 β -HSD1 inhibition (e.g., J2H-1702); CXCR4 antagonism; upstream stress-reduction strategies, including CBT and MBSR.
VN-ACh signaling: systemic vagal regulation and tumor-local cholinergic signaling	Acetylcholine; nAChRs, including α 5-nAChR; mAChRs, particularly CHRM3; cholinergic anti-inflammatory pathway.	Context-dependent effects: preserved vagal regulation may restrain excessive systemic inflammation, whereas reduced vagal tone may promote chronic low-grade inflammation. Tumor-local ACh signaling may suppress CD8 ⁺ T-cell IFN- γ production and promote PD-L1 expression, tumor invasion, and immune escape.	Preserved vagal regulation may maintain inflammatory homeostasis, whereas reduced vagal tone or tumor-local cholinergic signaling may promote a cold, immunosuppressive TME and reduce ICI sensitivity.	HRV-based assessment and biofeedback; CBT; MBSR; taVNS; CHRM3 antagonists, including solifenacin and darifenacin; selected experimental vagal-modulation strategies.
Tumor-infiltrating nerves	NE; ACh; NPY; neuropeptides; NGF; BDNF; Trk receptors; β -ARs; cholinergic receptors.	Axonogenesis; local neuroimmune crosstalk; neurotransmitter accumulation; stromal remodeling; angiogenesis; metabolic reprogramming and immune suppression.	May sustain local adrenergic or cholinergic immunosuppression and thereby reduce ICI sensitivity; direct evidence remains predominantly preclinical.	Trk inhibition; β -AR or cholinergic-receptor blockade; experimental chemical, surgical, or local neural denervation, alone or in combination with ICIs.

Note: The effects of vagal and cholinergic signaling are context-dependent and may vary according to tumor type, anatomical location, vagal tone, neurotransmitter source and receptor-expression pattern. Candidate interventions listed here should be interpreted as potential neuroimmune-modulating strategies; many remain supported primarily by preclinical, retrospective or early-stage clinical evidence and require prospective validation. Abbreviations: ACh, acetylcholine; ACTH, adrenocorticotropic hormone; AR, adrenergic receptor; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CBT, cognitive behavioral therapy; CHRM3, M3 muscarinic acetylcholine receptor; CREB, cAMP response element-binding protein; CRH, corticotropin-releasing hormone; CXCR4, C-X-C chemokine receptor 4; DPP4, dipeptidyl peptidase 4; GC, glucocorticoid; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; HRV, heart-rate variability; ICI, immune checkpoint inhibitor; IFN, interferon; MBSR, mindfulness-based stress reduction; MDSC, myeloid-derived suppressor cell; mAChR, muscarinic acetylcholine receptor; NE, norepinephrine; NGF, nerve growth factor; nAChR, nicotinic acetylcholine receptor; NPY, neuropeptide Y; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PKA, protein kinase A; RUNX, runt-related transcription factor; SNS, sympathetic nervous system; taVNS, transcutaneous auricular vagus nerve stimulation; TME, tumor microenvironment; TNF, tumor necrosis factor; Treg, regulatory T cell; Trk, tropomyosin receptor kinase; TSC22D3, TSC22 domain family member 3; 11 β -HSD1, 11 β -hydroxysteroid dehydrogenase type 1.

tional approaches. The principal pharmacological strategy is β -AR blockade, which competitively or noncompetitively reduces catecholamine signaling, particularly through β 2-AR, and may reverse immunosuppressive remodeling of the TME [103, 104]. β -Blockers under investigation can be broadly categorized as nonselective or β 1-selective agents.

Nonselective β -blockers

Propranolol is the most extensively studied nonselective β -blocker and inhibits both β 1-AR and β 2-AR. Proposed antitumor mechanisms include inhibition of angiogenesis, reversal of catecholamine-induced suppression of T-cell metabolism and function, reduction of M2-like macrophage polarization, and direct induction of apoptosis in selected β -AR-expressing tumor cells [105]. Propranolol may also stabilize p53 by counteracting AKT-MDM2-mediated degradation, thereby enhancing apoptosis and sensitivity to agents such as SN-38 [51-54]. Preclinical studies and retrospective clinical analyses suggest that nonselective β -blockers may improve outcomes when combined with chemotherapy or immunotherapy or used in perioperative settings across several solid tumors [57, 58, 106-110]. These associations require confirmation in prospective, tumor-specific trials.

β 1-selective blockers

Metoprolol and atenolol preferentially inhibit β 1-AR and have less effect on airway β 2-AR. They may therefore offer a safer profile for selected patients with cancer and coexisting chronic obstructive pulmonary disease (COPD) or asthma [111]. Some β 1-selective agents, such as atenolol, are relatively hydrophilic and exhibit limited penetration of the blood-brain barrier [112]. This pharmacokinetic property results in lower central exposure than that observed with lipophilic β -blockers such as propranolol and may help reduce certain neuropsychiatric adverse effects, although the clinical relevance of this difference remains to be fully established [113]. This pharmacokinetic profile may offer a clinical advantage when minimizing central drug exposure is desirable. In experimental models, β 1-selective blockade limits terminal differentiation of exhausted CD8⁺ T cells and increases IFN- γ and TNF production [13]. Exploratory data from EORTC

1325/KEYNOTE-054 further support evaluation of β 1-selective blockers as adjuncts to pembrolizumab [42]. However, these findings remain preliminary because β -blocker exposure was not randomized, exposure misclassification was possible, and the small number of patients receiving specific β -blocker subclasses limited further statistical analyses. Prospective studies are therefore required to confirm the clinical benefit.

Nonpharmacological approaches

Nonpharmacological modulation of the SNS-NE- β -AR axis includes behavioral interventions and physical interruption of neural signaling. Mindfulness practices, such as breathing exercises, meditation, and movement-based training, may reduce sympathetic tone and increase parasympathetic activity, although direct mechanistic evidence linking these changes to improved ICI efficacy remains limited [114]. Physical approaches, including 6-OHDA-mediated local denervation or Trk-receptor blockade, reduce stress-induced tumor innervation and improve ICI activity in preclinical models [48, 49]. Surgical or chemical interruption of sympathetic adrenergic nerves has also inhibited tumor initiation in prostate-cancer models [36]. Conversely, EE can activate distinct SNS programs, suppress CCL2 expression, and overcome PD-L1 resistance in experimental settings [13].

Modulating the HPA-GC axis

Pharmacological Inhibition of GC signaling, synthesis, and regeneration

Pharmacological strategies are being explored to mitigate T-cell dysfunction by limiting systemic GC synthesis, local GC regeneration, or GR signaling. Mifepristone antagonizes GR and has reversed stress-associated reductions in chemotherapy efficacy in experimental models [2]. Metyrapone inhibits adrenal GC synthesis and may attenuate depression-associated immune dysregulation [67]. Inhibition of 11 β -HSD1 with agents such as J2H-1702 prevents local conversion of inactive metabolites into active GCs, reduces M2-like macrophage polarization, and enhances anti-PD-1 responses in preclinical systems [32, 80, 81].

Upstream intervention may also have translational value. Metyrapone-mediated suppres-

sion of systemic GC synthesis and CXCR4 antagonism have improved responses to ICIs in experimental settings [2, 67, 77]. Because GC secretion follows a pronounced circadian rhythm, chronotherapeutic scheduling that avoids endogenous GC peaks may reduce interference with T-cell activation, proliferation, and differentiation [115, 116]. These approaches require prospective evaluation to determine dosing, timing, safety, and interaction with standard anticancer therapy.

Nonpharmacological approaches

CBT and MBSR are widely used supportive nonpharmacological interventions in oncology. Both may lower perceived stress, modulate HPA-axis activity, and influence autonomic and neuroimmune regulation [68, 82, 83, 98]. Evidence that CBT reduces cortisol in patients with cancer remains limited, although systematic reviews of cognitive behavioral stress management (CBSM) have identified changes in selected biobehavioral markers [83, 117].

Neuroendocrine evidence is somewhat broader for MBSR and related mindfulness-based interventions (MBIs). Some studies have reported improvements in negative affect and reductions in cortisol levels after mindfulness training [118-120]. Others have found no significant changes [121-123]. Differences in intervention content, adherence, sampling time, cortisol-assay methods, and participant characteristics may contribute to this heterogeneity. Standardized protocols and adequately powered trials are needed before endocrine effects can be considered established.

Modulating VN-ACh signaling

Pharmacological targeting of cholinergic receptors and downstream pathways

Pharmacological interruption of tumor-promoting cholinergic signaling is being investigated as a means of reducing immune tolerance. Stress-responsive vagal signaling and tumor-cell autocrine production can increase local ACh. CHRM3 antagonists, including solifenacin and darifenacin, have been proposed as combination partners for anti-PD-L1 therapy [94, 96, 124]. In gastric cancer, ACh released by infiltrating vagal fibers can activate a lipid-metabolic pathway involving alpha/beta hydro-

lase domain-containing protein 16A (ABHD16A) and lysophosphatidylserine (LysoPS), thereby inducing PD-L1 expression and immune escape [38]. Small molecules such as darifenacin and BTB09089 may target this neuroimmune-metabolic network and enhance anti-PD-1/PD-L1 activity, although clinical evidence is not yet available [38].

Psychological and physical restoration of vagal anti-inflammatory tone

Nonpharmacological neuromodulation seeks to integrate psychological and physiological care. In experimental studies, taVNS has remodeled neuroimmune signaling, increased intratumoral CD8⁺ T-cell density, and increased IFN- γ expression [101]. These findings suggest that taVNS may have potential as a noninvasive adjunct for stress-associated immune dysfunction. However, oncological applications remain at an early stage, and neural stimulation has not consistently produced measurable tumor-growth inhibition [101, 110, 125].

MBSR may improve psychological resilience and could interrupt the pathway linking reduced vagal tone to chronic low-grade inflammation, although direct anticancer effects remain uncertain because of population and intervention heterogeneity [19, 102]. Experimental surgical, chemical, or electrical modulation of vagal pathways has attenuated systemic wasting and, in some models, enhanced the effects of chemotherapy [19, 91, 96, 97]. Because these interventions can affect broad autonomic functions, their anatomical specificity and safety require rigorous evaluation.

HRV biofeedback training is a feasible supportive intervention for chronic symptoms among breast-cancer survivors, including anxiety, stress, insomnia, menopausal symptoms, and cognitive complaints [125]. Nevertheless, few preclinical or clinical studies have directly tested whether nonpharmacological vagal interventions synergize with anti-PD-1/PD-L1 therapy to suppress tumor growth. This evidence gap should be addressed before routine integration into immunotherapy protocols.

Conclusions and future perspectives

This review synthesizes evidence that negative psychological factors, including CPS, depres-

sion, and anxiety, may engage peripheral neuroendocrine-immune pathways, remodel the TME, and influence the efficacy of immunotherapy. Three interconnected systems are central to the proposed framework. Stress-associated SNS activation increases NE and engages β 1-, β 2-, and β 3-AR signaling; prolonged HPA activation elevates circulating GCs and may be amplified locally by 11 β -HSD1; and anxiety- or depression-associated reductions in vagal tone may weaken systemic cholinergic anti-inflammatory control, while tumor-local ACh signaling can promote immune escape. Collectively, the available evidence supports the interpretation that psychological distress may be a biologically relevant modifier of treatment response rather than merely a comorbidity of cancer. β -Adrenergic blockade, inhibition of intratumoral glucocorticoid regeneration, glucocorticoid receptor antagonism, and blockade of selected cholinergic pathways may enhance ICI efficacy, although the evidence remains largely preclinical [2, 13, 49, 51, 57, 58, 67, 77, 94, 96, 106-110, 124]. Among these strategies, β -blockade has received the greatest clinical attention; nevertheless, current observational and early-phase clinical data are insufficient to establish a consistent therapeutic benefit.

Although discussed separately for clarity, the SNS, HPA-GC, and VN-ACh pathways are unlikely to function as completely independent systems. Psychological stress can concomitantly activate sympathetic and HPA responses, leading to coordinated increases in NE and GC signaling [4, 5]. NE- and GC-mediated signals may subsequently converge on overlapping immune-cell populations and potentially reinforce immunosuppressive remodeling of the TME [13, 32, 76, 77]. VN-ACh signaling may further modify this neuroendocrine-immune balance. Under some conditions, preserved vagal activity may counteract excessive inflammatory responses [87-90]. In specific tumor contexts, however, local cholinergic signaling can promote immune escape [93-96]. Thus, the net neuroendocrine influence on tumor immunity may reflect the relative balance among sympathetic, glucocorticoid, and cholinergic signals rather than the activity of any single pathway. However, the direction, magnitude, and clinical relevance of these interactions remain insufficiently defined.

Several barriers must be addressed before these findings can be translated into routine care. First, much of the clinical evidence for β -blockers and related agents is retrospective and is confounded by dose, timing, indication, drug selectivity, and tumor-type heterogeneity [59, 60]. Second, most studies still evaluate individual neural axes in isolation, limiting an integrated understanding of neuroendocrine-immune regulation. Third, the reliability and clinical utility of candidate psychobiomarkers, including HRV and CLOCK expression, remain uncertain [55, 98, 102]. Fourth, tumor types differ substantially in their patterns of innervation, and the mechanisms by which non-pharmacological interventions might improve ICI responses in psychologically distressed patients remain poorly defined. Finally, the mechanisms and clinical implications of combining psychotropic drugs with immunotherapy require systematic investigation.

Future research should prioritize prospective evaluation of β -blockers, inhibitors of GC synthesis or metabolism, cholinergic-receptor antagonists, and selected psychotropic agents in rational combinations with ICIs. Mechanistic studies should define interactions among neural axes and clarify the tumor-specific roles of β 3-AR, autocrine ACh signaling, and neuro-metabolic reprogramming, including glycolysis and lipid metabolism. Multicenter prospective trials should develop and validate multidimensional psychobiomarker panels that integrate psychological measures with autonomic, endocrine, and immune variables to identify patients most likely to benefit from neuroendocrine-immune interventions. In addition, research should extend beyond negative affect to determine how EE and other beneficial stimuli engage distinct neural circuits and enhance antitumor immunity [13]. Trials integrating psychological interventions, physical neuromodulation, and pharmacological blockade may ultimately support a more comprehensive biopsychosocial approach to cancer treatment.

In conclusion, elucidating psychological-neural-immune interactions may deepen understanding of cancer as a systemic disease and provide a scientific basis for individualized combination strategies. Integrating psychological care with tumor immunology could comple-

ment current treatment paradigms and support the development of more comprehensive, mechanism-informed cancer care.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (82573690), the Sanming Project of Medicine in Shenzhen (SZSM202411029) and the Shenzhen Natural Science Foundation's General Project (JCYJ20240813145301002 and JCYJ20250604183455074).

Disclosure of conflict of interest

None.

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