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CHRONIC STRESS AS A MODULATOR OF THE TUMOR IMMUNE MICROENVIRONMENT

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Abstract. Chronic psychological stress is increasingly recognized as a biological modifier of cancer progression through sustained neuroendocrine and immune dysregulation. This narrative review summarizes current evidence on how chronic activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system reshapes the tumor immune microenvironment and may influence response to anticancer therapy. Glucocorticoid and adrenergic signaling can alter immune-cell trafficking, differentiation, metabolism, and effector function, promoting expansion or functional reprogramming of tumor-associated macrophages, myeloid-derived suppressor cells, and neutrophils while impairing cytotoxic T-cell and natural killer-cell activity. Experimental studies provide particularly strong evidence for glucocorticoid-dependent neutrophil reprogramming and neutrophil extracellular trap

formation as mechanisms linking chronic stress with prometastatic microenvironmental changes. Persistent beta-adrenergic signaling may additionally promote metabolic dysfunction and exhaustion of tumor-infiltrating T cells. Emerging clinical studies in melanoma and non-small-cell lung cancer have associated pretreatment emotional distress with inferior outcomes during immune checkpoint blockade; however, these observations remain non-causal. Current evidence supports chronic stress as a potentially modifiable component of tumor-immune interactions, but prospective mechanistic and interventional studies are required before stress-related parameters or adrenergic modulation can be used as validated predictive or therapeutic tools in oncology.

Keywords: chronic stress; tumor immune microenvironment; neuroendocrine signaling; glucocorticoids; adrenergic signaling; neutrophil extracellular traps; immune checkpoint blockade; cancer immunotherapy.

Introduction

Chronic psychological stress is increasingly recognized as a potential biological modifier of cancer progression rather than solely a psychosocial consequence of malignant disease. Persistent activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system leads to prolonged exposure to glucocorticoids and catecholamines, which can influence both tumor cells and multiple components of the tumor microenvironment [1, 2, 5].

Neuroendocrine stress signaling may alter the recruitment, differentiation, and functional activity of immune cells within tumors. Particular attention has been focused on stress-associated changes in tumor-associated macrophages, myeloid-derived suppressor cells, neutrophils, natural killer cells, and cytotoxic T lymphocytes [1, 2]. These effects may contribute to the establishment of an immunosuppressive microenvironment characterized by impaired antitumor immune surveillance, enhanced inflammatory signaling, and conditions that favor tumor growth and dissemination.

Experimental studies indicate that chronic adrenergic and glucocorticoid signaling can influence immune-cell trafficking, myeloid-cell polarization, neutrophil activation, and formation of neutrophil extracellular traps (NETs), while simultaneously impairing effective T-cell- and NK-cell-mediated antitumor responses [2, 4, 6]. Such mechanisms provide a biological link between chronic stress and tumor immune escape.

The clinical relevance of these interactions is of particular interest in the era of immunotherapy. Preclinical and translational evidence strongly supports stress-associated modulation of antitumor immunity, while emerging clinical studies have reported associations between pretreatment emotional distress and inferior responses or outcomes during immune checkpoint blockade in melanoma and non-small-cell lung cancer [8, 9]. However, these observational associations do not establish causality, and the extent to which neuroendocrine stress signaling independently determines immunotherapy response remains uncertain.

Aim and Objectives

Aim: to summarize current evidence on the mechanisms through which chronic stress modifies the tumor immune microenvironment and to assess the potential implications of neuroendocrine-immune interactions for tumor progression and response to anticancer therapy.

Objectives:

1. To characterize the principal neuroendocrine pathways through which chronic stress influences antitumor immunity, with particular attention to glucocorticoid and adrenergic signaling.
2. To analyze stress-associated remodeling of myeloid and lymphoid compartments of the tumor microenvironment, including tumor-associated macrophages, myeloid-derived suppressor cells, neutrophils/NETs, cytotoxic T lymphocytes, and natural killer cells.
3. To assess translational and clinical evidence linking stress-related neuroendocrine-immune changes with tumor progression and outcomes during immune checkpoint blockade, and to evaluate the current status of stress-pathway modulation as a therapeutic strategy.

Results and Discussion

Receptor-Level Neuroendocrine Signaling

Chronic stress influences antitumor immunity through sustained activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, resulting in prolonged exposure to glucocorticoids and catecholamines. These mediators act not only on malignant cells but also on multiple immune-cell populations within the tumor microenvironment. Because adrenergic and glucocorticoid receptors are expressed by cells of both innate and adaptive immunity, persistent neuroendocrine signaling can simultaneously influence immune-cell trafficking, differentiation, cytokine production, metabolic activity, and effector function [1, 2, 5]. This provides a biological framework in which chronic stress may reshape the tumor microenvironment at several interconnected levels rather than through a single immunological pathway.

Adrenergic signaling appears particularly relevant to this process. Persistent activation of beta-adrenergic pathways has been associated with reduced antitumor immune activity and altered functional states of tumor-infiltrating leukocytes [5, 6]. Experimental data indicate that chronic beta-adrenergic signaling can suppress T-cell receptor signaling and impair the metabolic fitness of tumor-infiltrating T lymphocytes. Conversely, pharmacological beta-adrenergic blockade or deletion of beta2-adrenergic receptors in experimental models was associated with increased glycolysis and oxidative phosphorylation, enhanced CD28 expression and cytokine production, and a reduction in exhausted T-cell phenotypes [6]. These findings suggest that neuroendocrine stress signaling may affect antitumor immunity not only by changing immune-cell abundance but also by directly altering cellular metabolism and functional competence.

Glucocorticoid receptor signaling provides a complementary pathway through which chronic stress can reprogram the immune microenvironment. Sustained

glucocorticoid exposure can alter transcriptional programs in myeloid cells and modify neutrophil activation, trafficking, reactive oxygen species generation, and NET formation [4, 10]. In the 2026 study of gastric cancer liver metastasis, glucocorticoid-dependent neutrophil activation was accompanied by an immunosuppressive hepatic niche characterized by neutrophil accumulation, impaired CD8⁺ T-cell effector function, and enhanced T-cell exhaustion; pharmacological inhibition of glucocorticoid receptor signaling or disruption of the neutrophil-NET pathway attenuated stress-associated metastatic progression [10]. These data indicate that glucocorticoids should be considered not only systemic stress hormones but also direct regulators of immune-cell state within metastatic niches.

Adrenergic and glucocorticoid pathways are therefore best viewed as interacting components of a broader neuroendocrine network rather than as isolated mechanisms. Beta-adrenergic signaling can directly impair T-cell receptor signaling and metabolic competence [6], whereas glucocorticoid signaling can favor myeloid and neutrophil programs associated with immune suppression and metastatic niche formation [4, 10]. Their convergence provides a plausible mechanism by which chronic systemic stress is translated into persistent local changes in antitumor immunity.

Integrated Myeloid-Lymphoid Remodeling

A particularly important target of chronic stress is the myeloid compartment. Sustained adrenergic and glucocorticoid exposure may promote recruitment and functional reprogramming of tumor-associated macrophages and expansion of myeloid-derived suppressor cells, thereby favoring an immunosuppressive microenvironment [1-3]. In experimental breast cancer models, chronic psychological stress promoted formation of a pre-metastatic niche through mobilization of splenic MDSCs involving tumor-associated macrophage/CXCL1 signaling [3]. Such myeloid remodeling may suppress cytotoxic lymphocyte activity while simultaneously supporting angiogenesis, invasion, and metastatic dissemination. Thus, stress-related alterations in the myeloid compartment may serve as an important interface between systemic neuroendocrine signals and local tumor immune escape.

The neutrophil-NET axis provides an additional mechanistic link between chronic stress and metastatic progression. He et al. demonstrated that chronic stress increased lung metastasis from disseminated tumor cells in experimental models and markedly remodeled the pulmonary microenvironment, with increased neutrophil infiltration and fibronectin accumulation together with reduced T-cell infiltration [4]. Chronic stress also disrupted the normal circadian behavior of neutrophils and increased formation of neutrophil extracellular traps through glucocorticoid-dependent signaling. Importantly, neutrophil depletion, neutrophil-specific deletion of the glucocorticoid receptor, or enzymatic degradation of NETs with DNase I attenuated stress-associated metastatic progression [4]. These experiments provide unusually strong mechanistic evidence because manipulation of individual components of the pathway directly modified the metastatic phenotype.

Stress-associated immune remodeling also involves the adaptive and cytotoxic arms of antitumor immunity. Chronic neuroendocrine activation has been linked to impaired

cytotoxic T-cell and natural killer-cell activity and to an immune environment favoring tumor escape [1, 2]. The metabolic effects observed in tumor-infiltrating T cells are particularly relevant because effective antitumor responses require sustained bioenergetic capacity, T-cell receptor signaling, and effector cytokine production. Experimental evidence therefore supports a model in which chronic stress can impair adaptive immunity both directly through beta-adrenergic signaling in T cells and indirectly through expansion or reprogramming of suppressive myeloid populations [3, 6].

Importantly, these cellular effects are unlikely to operate independently. Experimental data support a network-level model in which stress-conditioned tumor-associated macrophages can facilitate MDSC recruitment through CXCL1-related signaling [3], while glucocorticoid-responsive neutrophils and NETs remodel metastatic niches [4, 10]. At the same time, chronic adrenergic signaling can reduce the metabolic fitness and effector capacity of tumor-infiltrating T cells [6]. The combined result is a feed-forward immunosuppressive state in which myeloid expansion, neutrophil activation, extracellular-trap formation, and impaired cytotoxic lymphocyte function may reinforce one another. Although this integrated sequence has not been demonstrated as a single linear pathway in patients, it provides a coherent framework for interpreting the convergent experimental findings across different tumor models.

Clinical Translation and Unresolved Questions

These mechanisms are potentially important for immune checkpoint blockade. An immunosuppressive tumor microenvironment characterized by dysfunctional cytotoxic lymphocytes, increased suppressive myeloid populations, and persistent adrenergic or glucocorticoid signaling could theoretically reduce the effectiveness of antitumor immune reactivation [2, 5, 6]. Importantly, emerging clinical observations are broadly consistent with this biological hypothesis, although they do not establish causality.

In a post hoc analysis of the PRADO trial in patients with stage IIIB-D melanoma receiving neoadjuvant immune checkpoint blockade, pretreatment emotional distress was associated with a lower major pathological response rate (46% versus 65%) and lower 2-year relapse-free survival (74% versus 91%) and distant metastasis-free survival (78% versus 95%) [8]. The association persisted after adjustment for selected established tumor-related biomarkers, but the study could not demonstrate that neuroendocrine stress signaling itself caused the poorer outcomes.

A similar clinical signal was observed in the prospective STRESS-LUNG study of 227 patients with advanced non-small-cell lung cancer receiving first-line immune checkpoint inhibitor-based treatment. Baseline emotional distress was present in 111 patients and was associated with significantly shorter median progression-free survival (7.9 versus 15.5 months; HR 1.73, 95% CI 1.23-2.43) [9]. These findings strengthen the clinical relevance of the stress-immunity hypothesis but remain observational; emotional distress may coexist with other biological, behavioral, and disease-related factors capable of influencing treatment outcomes.

More recent translational evidence further supports a stress-associated neutrophil pathway in humans. In patients with gastric cancer liver metastasis, higher perceived stress was associated with increased cortisol and circulating myeloperoxidase-DNA

levels and with shorter progression-free survival, while parallel experimental models demonstrated glucocorticoid-dependent neutrophil activation, NET formation, impaired CD8⁺ T-cell function, and enhanced T-cell exhaustion [10]. Although these observations require external validation, they provide an important translational bridge between experimentally defined stress pathways and clinically measurable neuroendocrine and immune markers.

Pharmacological modulation of adrenergic signaling represents another translational direction. A phase I study combining the non-selective beta-blocker propranolol with pembrolizumab in patients with locally advanced or metastatic melanoma demonstrated that beta-adrenergic blockade can be administered alongside immune checkpoint inhibition [7]. However, the small uncontrolled design does not allow conclusions regarding improvement in antitumor efficacy. Adrenergic blockade should therefore currently be regarded as an investigational strategy rather than an established component of immunotherapy.

The emerging clinical literature also raises the question of whether stress-related biomarkers could eventually complement conventional oncological risk assessment. Potential candidates include validated psychometric measures of emotional distress, circulating cortisol, NET-associated markers such as myeloperoxidase-DNA complexes, and immune phenotypes reflecting myeloid activation or T-cell dysfunction [8-10]. At present, however, none of these parameters is sufficiently validated for routine prognostic or predictive use. The available studies differ in cancer type, treatment setting, methods used to quantify stress, timing of biomarker collection, and clinical endpoints, limiting direct comparison and generalization.

Several unresolved methodological issues are particularly important for future translation. Emotional distress may correlate with tumor burden, performance status, sleep disturbance, concomitant medication use, systemic inflammation, and other host factors that can independently influence treatment outcomes. Reverse causation is also possible, because more aggressive disease may itself increase psychological distress. Consequently, prospective studies should combine repeated psychometric assessment with longitudinal endocrine and immune measurements rather than rely on a single pretreatment evaluation. Parallel analysis of cortisol dynamics, NET-related biomarkers, myeloid-cell states, and T-cell functional phenotypes may help determine whether stress-associated biological changes mediate, rather than merely accompany, differences in clinical outcome [8-10].

Interventional studies will also need to distinguish between two related but biologically different strategies: reduction of psychological stress and direct pharmacological modulation of stress-response pathways. The feasibility of combining beta-adrenergic blockade with immune checkpoint inhibition has been demonstrated in a small phase I study [7], whereas experimental models support targeting glucocorticoid receptor signaling or the neutrophil-NET axis [4, 10]. Whether either approach can improve immunotherapy efficacy, reduce metastatic progression, or benefit selected biomarker-defined patient subgroups remains unknown and should be tested in controlled prospective trials.

Taken together, current evidence supports a multilevel model in which chronic stress is translated into tumor-promoting immune changes through coordinated neuroendocrine signaling. Glucocorticoid and adrenergic pathways can remodel myeloid populations, promote neutrophil and NET activity, impair T-cell metabolic fitness and effector function, and ultimately favor an immunosuppressive and prometastatic microenvironment. Importantly, the evidence base now extends beyond experimental models to observational and translational studies in patients with melanoma, non-small-cell lung cancer, and metastatic gastric cancer [8-10]. Nevertheless, these clinical associations cannot establish causality, and stress-related biomarkers should not yet be considered validated predictors of immunotherapy efficacy or cancer prognosis.

Conclusions

1. Chronic stress may modify the tumor immune microenvironment through sustained activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, with glucocorticoids and catecholamines acting as major mediators of neuroendocrine-immune interactions [1, 2, 5].

2. Stress-associated immune remodeling involves multiple cellular compartments, including tumor-associated macrophages, myeloid-derived suppressor cells, neutrophils, cytotoxic T lymphocytes, and natural killer cells. These coordinated changes may promote immunosuppression, weaken antitumor immune surveillance, and facilitate tumor progression [1-4, 6].

3. The neutrophil-NET axis and beta-adrenergic T-cell dysfunction represent two of the most strongly supported mechanistic links between chronic stress and impaired antitumor immunity. Their integration with TAM/MDSC remodeling suggests that stress-related immune suppression is a network-level phenomenon involving coordinated changes in innate and adaptive immune compartments [3, 4, 6, 10].

4. Emerging clinical and translational evidence suggests that pretreatment emotional distress and stress-associated biological markers may be relevant to outcomes during immune checkpoint blockade and metastatic progression [8-10]. However, heterogeneity of stress assessment, biomarker timing, tumor type, treatment context, and potential confounding prevents these parameters from being considered validated prognostic or predictive biomarkers.

5. Stress-associated neuroendocrine pathways remain biologically plausible but investigational therapeutic targets. Beta-adrenergic blockade has shown clinical feasibility, while preclinical and translational data support glucocorticoid receptor and neutrophil-NET pathways as additional candidates [4, 7, 10]. Future prospective trials should integrate longitudinal psychometric, endocrine, and immune measurements with predefined oncological endpoints to determine whether modification of stress-response pathways can produce clinically meaningful improvements in antitumor immunity and treatment outcomes.

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