

Review

State of the science: psychological stress, immune function, and future nursing interventions in nasopharyngeal carcinoma patients undergoing chemoradiotherapy

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Abstract: Psychological stress is a widespread health threat that modulates immune function via neuroendocrine pathways. In nasopharyngeal carcinoma (NPC) patients undergoing chemoradiotherapy, this interplay is clinically significant, potentially affecting treatment tolerance, complications, and survival. This narrative review summarizes the mechanisms and recent advances in nursing interventions. Chronic stress activates the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, elevating glucocorticoids and catecholamines, which suppress natural killer cell activity, disrupt T cell subsets, and promote a chronic inflammatory microenvironment with elevated interleukin 6 and tumor necrosis factor alpha. Chemoradiotherapy itself causes myelosuppression and immune cell reduction, and psychological stress may further aggravate immune dysfunction. Clinical evidence indicates that NPC patients with pretreatment anxiety or depression have lower 5 year survival rates, and cancer related fatigue correlates with neutrophil to lymphocyte ratio and high sensitivity C reactive protein. Preliminary studies suggest that psychoneuroimmunology based nursing interventions—including psychological screening, graded care, mindfulness based stress reduction, cognitive behavioral therapy, exercise rehabilitation, and combined nutrition psychological strategies—may modulate immune function. Future research should pursue NPC specific longitudinal mediation analyses, explore biomarkers, develop standardized protocols, and clarify the role of psychological care in immunotherapy. Clinical recommendations include routine screening, graded intervention, an integrated “psychology nutrition exercise” pathway, telehealth support, and enhanced nurse training. Incorporating systematic stress management into routine care may help break the “stress-immune suppression-poor outcomes” cycle and facilitate a transition toward mechanism-based, precision nursing, ultimately improving patients’ quality of life and prognosis.

Keywords: psychological stress; nasopharyngeal cancer; immune function; nursing intervention; psychoneuroimmunology

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor that originates from the mucosal epithelium of the nasopharynx. It has a unique geographical distribution pattern, being particularly prevalent in the southern part of China and Southeast Asian countries [1]. Radiotherapy is the preferred radical treatment for NPC, and the application of concurrent chemoradiotherapy (CCRT) has further improved the survival rate of patients with locally advanced disease [2]. However, radiotherapy and chemotherapy, while effectively killing tumor cells, also trigger a series of physiological and psychological stress responses [3], which not only reduce the patient’s treatment tolerance but also significantly affect their quality of life during

and after treatment, becoming a major concern in the diagnosis and treatment process of NPC patients.

Stress is ubiquitous in modern society and can be categorized into acute and chronic forms. Acute stress (e.g., exercise, cold exposure) rapidly triggers adaptive responses that help maintain homeostasis and enhance physiological functions [4]. In contrast, chronic stress—resulting from long-term, unrelieved stressors—continuously disrupts endocrine function and behavioral responses, thereby promoting the onset and progression of various diseases [5]. During the prolonged course of radiotherapy and chemotherapy for NPC, patients face multiple stressors, most of which are chronic in nature. Unlike acute stress, these chronic stressors cannot be resolved by the body's adaptive mechanisms; instead, they persistently activate the neuroendocrine system, ultimately leading to immune dysfunction [6].

Psychological stress is closely associated with tumor initiation, progression, and prognosis, with its core mechanism primarily involving the regulation of the neuroendocrine and immune systems. Specifically, psychological stress can activate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), promoting abnormal increases in stress hormone levels such as cortisol and catecholamines [7]. These stress hormones can directly act on corresponding receptors on the surface of immune cells, inhibiting the activity of natural killer cells (NK cells) [8], disrupting the balance of T lymphocyte subgroups [9], and promoting the release of inflammatory factors (such as IL-6, TNF- α) through various pathways. As a result, they weaken the body's tumor immune surveillance and may even create a microenvironment favorable to tumor invasion and metastasis. For NPC patients undergoing chemoradiotherapy, the treatment itself has already caused damage to the immune system (such as bone marrow suppression leading to a decrease in white blood cells) [10]. The addition of psychological stress can further compromise immune function, which could in turn reduce treatment completion rates and increase the risk of complications such as infections. Whether psychological stress adversely affects long term survival in NPC patients remains to be established, as current evidence is primarily derived from retrospective or small sample studies. Larger longitudinal investigations are required to clarify these associations.

Nursing interventions grounded in the theory of psychoneuroimmunology have shown potential for modulating immune function in preliminary studies. However, studies on the association between psychological stress and immune function in patients with NPC undergoing radiotherapy and chemotherapy are mostly based on evidence from other cancer types, and there is relatively limited specific evidence for NPC. Additionally, existing nursing intervention studies are scattered and lack systematic integration. This article adopts a narrative review method, based on relevant literature in databases such as PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) regarding psychological stress, immune function, NPC radiotherapy and chemotherapy, and nursing intervention (searching until April 2026), to systematically sort out the above issues.

In this review, we present the relevant mechanisms of psychological stress regulation on the immune function of patients with NPC. Additionally, this article aims to provide scientific theoretical basis and practical references for the psychological care and immune recovery of nasopharyngeal cancer patients. Importantly, we propose specific directions for future nursing research and practice, including establishing a routine psychological stress screening and graded

intervention system, developing an integrated “psychology–nutrition–exercise” nursing pathway, advancing remote health support technologies, and strengthening oncology nurses’ competencies in psychological care.

2. The impact of psychological stress on the immune function and prognosis of patients with NPC

2.1. The direct impact of psychological stress on immune function indicators in patients

A study involving 126 patients [11] with NPC undergoing CCRT revealed significant differences in Symptom Checklist-90 (SCL-90) scores as well as CD3 and CD4 immune indicators before and after treatment (all $P < 0.05$). Furthermore, the total score of psychological adaptation after treatment was positively correlated with the CD3 immune indicator ($P < 0.05$), indicating that patients with better psychological adaptation exhibit relatively stronger T-lymphocyte immune function. Notably, immune indicators also varied according to demographic characteristics. Patients with different income levels showed differences in pre-treatment CD3 and CD4 levels ($P < 0.05$), and patients with different marital statuses exhibited differences in post-treatment CD4 and CD8 levels ($P < 0.05$). These findings suggest that social support and economic status may influence psychological adaptation, thereby affecting immune function.

Furthermore, the inhibitory effect of psychological stress on the immune function of cancer patients has been confirmed in various malignant tumors. The core mechanism of this effect is common and can provide important references for research on NPC. Zheng et al. [12] found that chronic psychological stress is an independent risk factor affecting the growth and metastasis of breast cancer. The primary mechanism is that chronic psychological stress promotes the formation of an immunosuppressive microenvironment in breast cancer, inducing the polarization of tumor-associated macrophages toward the M2 phenotype, thereby inhibiting the host’s anti-tumor immune response and accelerating tumor progression.

In a prospective, single-blind, randomized controlled trial involving 198 patients with gastric cancer, participants were randomly divided into an intervention group ($n = 99$) and a control group ($n = 99$) [13]. The intervention group received a 12 week structured program comprising cognitive behavioral therapy (CBT), psychological counseling, sleep hygiene education, melatonin supplementation, and sleep behavior training. The primary endpoints were patients’ psychological status and immune function at 3 months, assessed by the Hospital Anxiety and Depression Scale (HADS) score and the $CD4^+/CD8^+$ T cell ratio. The results showed that anxiety, depression, and perceived stress in the intervention group were significantly reduced, and sleep quality was markedly improved. Concurrently, immune function was significantly enhanced (the $CD4^+/CD8^+$ ratio decreased from 1.78 to 1.44, $P = 0.001$), and levels of inflammatory markers were lowered. This study confirmed that a combined psychological and sleep intervention can effectively improve the psychological state of cancer patients, enhance immune function, and contribute to better survival outcomes.

The inhibitory effect of psychological stress on the immune function of cancer patients is universal, and the immune function of NPC patients is more significantly affected by psychological stress due to multiple pressures such as physical pain, disease fear, and economic burden brought by long-term radiotherapy and chemotherapy. The influence mechanism is similar to that of breast cancer, gastric

cancer, and other malignant tumors, involving the disorder of the neuroendocrine-immune axis. Chronic stress can continuously activate the HPA axis and the SNS, promoting the increase of glucocorticoid and catecholamine stress hormones levels. These hormones directly act on the corresponding receptors on the surface of immune cells, inhibiting the activity of NK cells and the function of T lymphocytes, remodeling the tumor microenvironment (TME) and systematically weakening the immune surveillance ability [14].

2.2. The impact of psychological stress on tumor control and long-term survival

The influence of psychological stress on the long-term prognosis of patients with NPC is currently the topic of the highest research attention and has the most clinical translational value. A retrospective study [15] involving 358 patients who underwent radical radiotherapy for NPC showed that the 5-year overall survival rate of the entire group was 74.8%, but the 5-year overall survival rate of 142 patients who had anxiety before radiotherapy was only 64%, while that of 216 patients without anxiety was 82.5%. The difference of 18.5 percentage points is of significant clinical importance, suggesting that psychological state may be an independent prognostic factor involved in the treatment outcome of NPC.

Chronic stress can change the TME by continuously activating the HPA axis and the SNS, participating in various processes including tumor occurrence, progression, metastasis, and multiple drug resistance. The characteristic of the stress-induced TME is an increase in the proportion of pro-cancer immune cells and cytokines [16]. A new study has confirmed that mental stress can reprogram dendritic cells, inhibit anti-tumor immune responses, and ultimately lead to worse chemotherapy and immunotherapy effects [17]. Clinical studies have also shown that anxiety and depression are related to recurrence, metastasis, and poor prognosis, and adverse stress may worsen prognosis through immunosuppressive pathways [18,19]. Although most of this evidence comes from studies on pan-cancer types, their core mechanisms are highly similar to those of NPC, suggesting that the prognostic effect of psychological stress in NPC radiotherapy and chemotherapy deserves high attention.

3. The regulatory mechanism of psychological stress on immune function

3.1. Neuroendocrine pathways: the HPA axis and the SNS

The two core pathways that regulate immune function in response to stress are the HPA axis and the SNS [20]. These two pathways are highly conserved evolutionarily and together form the core endocrine response system of the body in response to stress.

The activation of the HPA axis begins with the secretion of corticotropin-releasing hormone (CRH) by the paraventricular nucleus of the hypothalamus [21]. CRH stimulates the anterior pituitary to release adrenocorticotrophic hormone (ACTH), which in turn prompts the adrenal cortex to synthesize and secrete glucocorticoids (GCs) [21]. In humans, the main glucocorticoid is cortisol. The continuous activation of the HPA axis is one of the core mechanisms by which chronic stress affects the immune system. Persistent stressors cause the HPA axis to remain in a state of continuous excitation, maintaining elevated levels of GCs in the body for a long time, thereby exerting extensive inhibitory effects on the immune system [22,23].

The SNS is activated under chronic stress conditions. The hypothalamus activates sympathetic ganglion-preceding neurons through brainstem nuclei (such as the locus coeruleus) and subsequently stimulates the release of catecholamine hormones from the adrenal medulla – mainly adrenaline and noradrenaline [24]. Additionally, the terminals of the sympathetic nerves can directly release noradrenaline to act on peripheral tissues. Catecholamine hormones rapidly regulate the functional state of immune cells through their binding to β -adrenergic receptors (β -ARs) on the surface of immune cells, such as activating eosinophils in the skin to exacerbate skin inflammation [25].

It is worth noting that the HPA axis and the SNS do not operate independently but rather interact with each other at multiple levels of the central nervous system to jointly regulate the stress response. CRH is not only the upstream initiating factor of the HPA axis but also activates the SNS and the 5-hydroxytryptamine system at the central level, forming a multi-pathway integrated stress response network [21,26]. The two pathways shape the immune landscape of the body under chronic stress conditions through different time scales of signal transmission-the HPA axis functions through the hormonal pathway (with slower but longer-lasting effects), while the SNS responds rapidly through the neurotransmitter pathway-jointly creating a microenvironment conducive to the occurrence and development of tumors 29.

3.2. Chronic inflammatory microenvironment induced by stress

Chronic stress not only directly inhibits the function of anti-tumor immune cells but also induces a persistent and low-level systemic inflammatory response, creating a favorable microenvironment for the occurrence and development of tumors [27]. Under normal physiological conditions, the serum IL-6 level is below 10 pg/mL, while the IL-6 level in saliva is approximately 10 pg/mL [28,29]. IL-6 is expressed at high levels in the serum and TME of cancer patients. IL-6 originates from immune cells infiltrating cancer (including TAMs, myeloid-derived suppressor cells (MDSCs), monocytes, and granulocytes), stromal cells (such as fibroblasts and adipocytes), and cancer cells [30]. Research evidence by Wang et al. indicates that chronic stress can activate intracellular pro-inflammatory transcription factors in immune cells, mediating the release of pro-inflammatory cytokines such as IL-6 [31].

The transcription and secretion of pro-inflammatory factors depend on the two signaling pathways, STAT-3 and NF- κ B. After the stress hormone binds to the corresponding receptors on the surface of inflammatory cells, it can activate these two signaling pathways [32,33]. IL-6 in the TME promotes the excessive activation of STAT-3 and NF- κ B in cancer cells through autocrine and paracrine pathways, forming an IL-6 positive feedback loop, which mediates cancer progression and invasion [30]. This self-sustaining inflammatory environment has multiple effects: in inflammatory cells, it maintains a chronic inflammatory state; in pre-cancerous cells, it acts as a carcinogenic transcription factor to promote tumor initiation; in tumor-infiltrating immune cells, it acts as a pro-differentiation transcription factor to promote tumor progression.

Under chronic stress conditions, the increase in pro-inflammatory cytokine levels is also closely related to DNA damage, changes in epigenetic modifications, and remodeling of the TME. These changes collectively constitute the molecular basis for stress promoting tumor occurrence and progression. In addition, IL-6 is expressed at higher levels in various epithelial tumors, and its level is positively correlated with the poor prognosis of patients [34,35]. The inflammatory state

induced by chronic stress is particularly crucial in the TME. Stress hormones not only systemically weaken the immune surveillance function but also directly reshape the cell composition and functional characteristics of the TME, manifested as an increase in the proportion of pro-cancer immune cells (such as the M2 polarization of tumor-associated macrophages) and pro-inflammatory cytokines [36]. This remodeling makes tumor cells more prone to evade recognition and clearance by the host immune system, accelerating tumor progression and metastasis.

4. Nursing under the background of radiotherapy and chemotherapy

Chemoradiotherapy itself constitutes a potent physiological stressor. Physiological stressors such as pain, fatigue, and malnutrition during treatment can further activate the secretion of stress hormones via the hypothalamic-pituitary-adrenal (HPA) axis and the SNS [37], thereby establishing a vicious cycle of “treatment stress → immune suppression → reduced treatment tolerance”. Consequently, in the immunological management of patients with NPC undergoing chemoradiotherapy, psychological stress should be systematically evaluated and addressed as a potential key variable that may influence immune function and treatment outcomes. However, direct causal evidence in NPC patients is still limited, and further prospective studies are needed. Organs in the head and neck region are not only essential for daily functions but also carry significant social implications. Therefore, patients with head and neck cancer often face greater physical, emotional, and psychological challenges. Side effects of chemoradiotherapy – including oral mucositis, painful swallowing, xerostomia, and taste alterations – not only cause persistent physical distress but also directly interfere with basic eating functions, leading to malnutrition and weight loss. Nutritional status itself is a critical determinant of immune function. A systematic review and meta-analysis protocol has highlighted that the impact of non-pharmacological interventions on the nutrition and immune status of NPC patients undergoing chemoradiotherapy has become a research focus, suggesting an intrinsic link between nutrition and immunity in NPC care [38]. This intricate interplay of physiological, psychological, and immunological factors renders the care of NPC patients far more complex than that of general oncology patients.

The rehabilitation of quality of life has become equally important as survival prolongation. With the marked improvement in survival rates among NPC patients, these individuals now commonly face new challenges in achieving life rehabilitation. Maximizing the maintenance and restoration of post-treatment quality of life and social functioning has become a core clinical goal. Interventions targeting speech, swallowing, and appetite have been shown to facilitate better recovery in NPC patients [39]. Within this framework, the role of nursing extends beyond passively managing treatment side effects; it requires the active integration of psychological support, functional rehabilitation, and immune maintenance to establish a multidimensional care system.

Given the clear impact of psychological stress on immune function, systematic psychological assessment and graded nursing care are essential. Graded nursing care refers to matching intervention resources to different levels of psychological distress, thereby achieving precise and efficient care. The recommended grading criteria are as **Table 1**.

Table 1. Graded nursing intervention for psychological distress in NPC patients undergoing chemoradiotherapy.

Grade	Assessment criteria (using Distress Thermometer, DT)	Intervention	Provider
Level I (Universal psychological support)	DT < 4, no significant anxiety or depression	Routine supportive communication, disease education, optimization of treatment environment	Bedside nurse
Level II (Targeted psychological intervention)	DT ≥ 4 or mild anxiety/depression (HADS 8–11)	Structured group mindfulness training, CBT group, regular psychoeducation courses	Trained specialized nurse or psychotherapist
Level III (Specialized psychological treatment)	Moderate to severe anxiety/depression (HADS ≥ 11) or presence of suicidal risk	Individual psychotherapy (CBT, acceptance and commitment therapy [ACT]), psychiatric medication referral if necessary	Psychiatrist, clinical psychologist

Implementation recommendations: Assessments should be conducted at the following time points: baseline before treatment, during each hospitalization for chemotherapy, before the completion of radiotherapy, and at 3 and 6 months post treatment. The results should be documented in the nursing records and used to dynamically adjust the grade of care.

4.1. Structured psychological interventions: MBSR and CBT

Mindfulness-based stress reduction (MBSR) typically involves an 8-week program (2.5-hour weekly group sessions plus daily home practice). Meta-analyses in cancer patients have shown that MBSR reduces perceived stress, anxiety, and depression, and may enhance NK cell activity [40]. In a small NPC study, MBSR was observed to reduce the need for leukocyte-promoting drugs, suggesting potential mitigation of myelosuppression [41].

Cognitive-behavioral therapy (CBT) targets negative automatic thoughts and behavioral avoidance related to chemoradiotherapy. In a gastric cancer trial, CBT combined with sleep intervention significantly improved the CD4⁺/CD8⁺ ratio [42]. For NPC patients, CBT can be tailored to address catastrophic cognitions about painful swallowing and altered appearance [43]. It is generally delivered in weekly individual or group sessions for 6–12 weeks [44].

4.2. Exercise rehabilitation

Exercise rehabilitation refers to individualized physical activity prescriptions based on the patient's physical condition and safety assessment, aiming to maintain or improve cardiopulmonary function, muscle strength, and immune function. For NPC patients undergoing chemoradiotherapy, a graded, progressive approach is recommended:

- Acute phase (severe mucositis, platelets < 20 × 10⁹/L): Bed-anchored ankle pumps, seated stretching (5–10 minutes, twice daily).
- Recovery phase (symptom relief, platelets > 50 × 10⁹/L): Indoor slow walking (15–20 minutes daily), simplified Tai Chi.
- Maintenance phase (post-treatment): 150 minutes of moderate-intensity aerobic exercise (e.g., brisk walking, stationary cycling) per week, plus resistance training twice weekly.

Exercise promotes immune cell redistribution and increases NK cell activity while releasing endorphins to improve mood [45].

4.3. Enhancing oncology nurses' competence in psychological care

To enable the above interventions, systematic training is essential. The following pathway is suggested:

- Basic training (all oncology nurses): 4–6 hours covering mechanisms of stress-immune interaction, use of assessment tools (DT, HADS), basic listening and empathy skills, crisis recognition and referral. Assessment via objective structured clinical examination (OSCE).
- Advanced training (specialized nurses): 40 hours covering structured psychological interventions (basics of MBSR, CBT), group facilitation skills, case management. Those who pass the examination receive certification as “Oncology Psychosocial Nursing Specialist.”
- Ongoing supervision: Monthly group supervision led by a clinical psychologist or psychiatrist to discuss complex cases and prevent compassion fatigue.
- Interdisciplinary collaboration: Schedule dedicated psychological care time in nursing shifts (e.g., 30 minutes per nurse per day) and establish a green-channel referral system to the psychology department.

5. Future research directions and clinical recommendations

Current evidence linking psychological stress to tumor prognosis via immune pathways is derived predominantly from studies on breast cancer, lung cancer, or pan-cancer cohorts. Prospective longitudinal cohort studies specifically focusing on NPC patients receiving chemoradiotherapy remain scarce. Future research should employ large-sample, multi-center longitudinal designs that simultaneously collect psychological assessment data (perceived stress, anxiety, depression, fatigue), peripheral blood immune parameters (lymphocyte subsets, NK cell activity, inflammatory cytokine profiles), and clinical outcomes (treatment completion rate, complications, progression-free survival, overall survival) at multiple time points: before, during, and after chemoradiotherapy. Structural equation modeling or causal mediation analysis should be applied to quantitatively test the mediating effect of “psychological stress → immune alteration → prognostic difference” and to estimate its effect size. Such studies would provide the most direct causal evidence to support psychological nursing interventions.

Significant inter-individual variability exists in neuroendocrine and immune responses to the same stressor. Future research should focus on two categories of biomarkers: (1) susceptibility biomarkers – such as glucocorticoid receptor gene polymorphisms and β 2-adrenergic receptor genotypes – to identify patient subgroups that are more sensitive to psychological stress and more prone to immune suppression; and (2) intervention response biomarkers – such as salivary cortisol circadian rhythms and stress-induced changes in peripheral blood inflammatory cytokines – to predict which patients are more likely to benefit from psychological care interventions. Establishing biomarker-based stratification models would facilitate precision nursing and avoid inefficient resource allocation.

Given the well-established impact of psychological stress on immune function and its potential negative implications for prognosis, it is recommended that psychological stress assessment be incorporated as a routine component of comprehensive care for NPC patients undergoing chemoradiotherapy-on a par with vital signs and complete blood count monitoring. The Distress Thermometer (DT) can

be used for rapid screening, with a cut-off score of ≥ 4 indicating positive findings. For screen-positive patients, quantitative assessment using the HADS or the Perceived Stress Scale (PSS-10) is recommended. The assessment schedule should include at minimum: baseline before treatment, during each hospitalization for chemotherapy, before the completion of radiotherapy, and at 3- and 6-months post-treatment. Results should be documented in the nursing records and serve as the basis for individualized care planning.

6. Conclusion

In summary, psychological stress affects the immune function of NPC patients undergoing radiotherapy and chemotherapy through a clear neuroendocrine pathway, and is associated with treatment tolerance, complications, and survival prognosis. Nursing interventions grounded in the theory of psychoneuroimmunology may help disrupt the “stress $\rightarrow$ immune suppression $\rightarrow$ adverse outcome” vicious chain (**Figure 1**) and achieve a leap from empirical care to mechanism-based and precise care. Although preliminary findings are promising, further research is needed to confirm the efficacy of such interventions in NPC patients. The continuous exploration in this field will provide strong scientific support and practical paths for the ultimate goal of “living longer and better” for NPC patients.

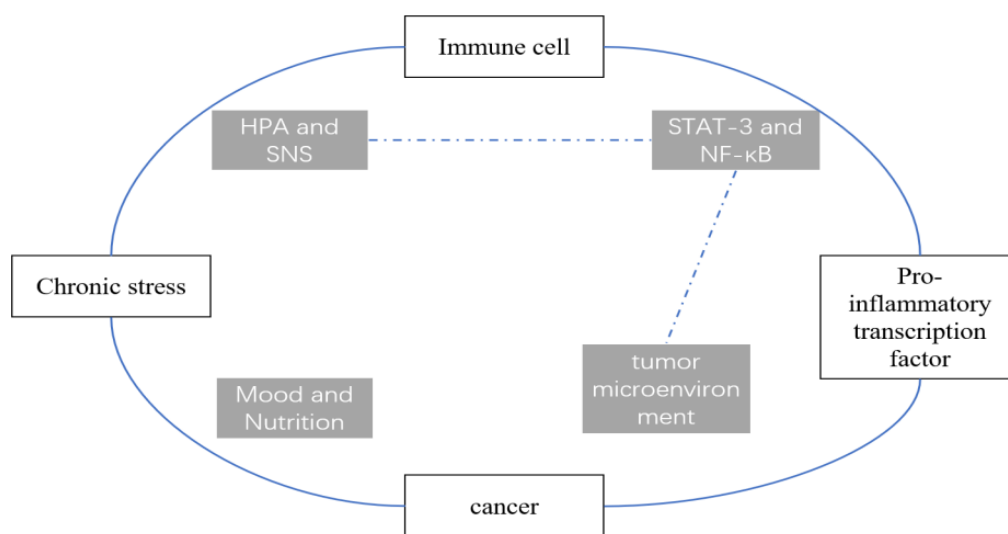


Figure 1. The interwoven network of physiology, psychology and immunity.

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