Stress and cancer: The mechanisms of immune dysregulation and management

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Advances in the understanding of psychoneuroimmunology in the past decade have emphasized the notion that stress and cancer are interlinked closely. Durable chronic stress accelerated tumorigenesis and progression, which is unfavorable for clinical outcomes of cancer patients. Available evidence has provided unprecedented knowledge about the role and mechanisms of chronic stress in carcinogenesis, the most well-known one is dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). With abnormal activation of neuroendocrine system, stress-related hormones contribute to increased oncogenes expression, exacerbated chronic inflammation and impaired immunologic function. In addition, accumulating studies have demonstrated that diverse stress interventions including pharmacological approaches, physical exercises and psychological relaxation have been administered to assist in mental disorders reduction and life quality improvement in cancer patients. In this review, we systematically summarize the connection and mechanisms in the stress-immune-cancer axis identified by animal and clinical studies, as well as conclude the effectiveness and deficiencies of existing stress management strategies.

KEYWORDS
chronic stress, hypothalamic-pituitary-adrenal axis, tumor microenvironment, immunity, stress management

Introduction

With the fast pace of living in today’s society, stress is becoming a common experience across the globe. Stress origins from various changes in social environment including interpersonal relationships, financial hardships and physiological diseases, leading to adaptive psychological and physiological changes (1–3). Depending on its duration and intensity, stress can be classified as acute (e.g., surgery, exercise, cold...
temperature) or chronic (e.g., social isolation, work stress, prolonged cancer treatment). Generally, acute stress can quickly mobilize adaptive response as a stimulant to maintain homeostasis, which is beneficial to the body. However, when stressors don’t subside for a long time, they will exert effects on the endocrine system and behavioral responses to participate in multiple diseases (4, 5). It is widely accepted that there are tight associations between stressful events and cancer. Chronic exposure to stressors promotes tumorigenesis and development. Meanwhile, some psychosomatic symptoms such as anxiety, fatigue, or depression during survivorship can also act as the sources of stress to exacerbate tumor progression (6–9).

The neuroendocrine system, the most comprehensively studied mediator that links stress and cancer, consists of the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) (2). Stress induces the release of three major hormones: epinephrine, norepinephrine and glucocorticoid. These stress-related hormones activate various cytokines secretion and molecular signaling pathways to remodel the tumor microenvironment (TME) through binding to adrenergic receptors (ARs) and glucocorticoid receptors (GRs) (1, 9). For example, behavioral stress-induced epinephrine accelerated tumor growth through β2AR/PKA/DAB pathway in a prostate-specific myc transgenic murine model (10). Similarly, chronic stress promoted norepinephrine secretion which induced VDCC phosphorylation and IGF2 exocytosis in lung epithelial cells to facilitate malignant transformation (11). As for the glucocorticoid, social defeat elevated the expression of glucocorticoid-inducible factor Tsc22d3, resulting in increased plasma corticosterone concentrations and damaged DC function (12). Besides, higher expression levels of GRs and glucocorticoid regulation kinases predicted poorer survival in breast cancer (13, 14).

Immunosuppression is one of hallmarks of TME. Most immune cells express β-ARs and GRs, they are the bridges to stress-induced immune function damage (15). Mounting animal studies have demonstrated that chronic stress could suppress cancer-related immune responses through altering various immune cells. In clinical researches, the metastatic breast cancer patients with more depressive symptoms showed higher plasma cortisol concentrations and suppressed immunity (16). Additionally, social isolation was associated with higher norepinephrine levels, while social support elevated the percentage of NK-T cells in ovarian cancer patients (17, 18). All of these researches indicate that there is a tight link between stress and tumor immunity.

In this review, we present a comprehensive interpretation of stress responses at organism level, and the interaction between stress and tumor immune microenvironment. In addition, we discuss the limitations and application perspectives of current stress management strategies in cancer patients.

Epidemiological association between stress and cancer

With the rapid pace of life, mental health of people is growingly concerned. Psychosomatic disturbance is more common among individuals diagnosed with cancer as compared to general population (19). For example, the prevalence of depression among cancer patients ranges from 15-30%, while the average rate of general population is about 3.3% (19). It is noteworthy that although limited number of studies and non-uniform diagnosis standards (self-assessment report, symptom detection, or person-to-person interview) cause results heterogeneity, the incidence of psychologic disorders in cancer patients has gradually increased (20).

Psychological stress level reaches the first peak at the time of cancer diagnosis and psychosomatic symptoms containing anxiety, fatigue, insomnia even depression subsequently develop over the next year (21,22). In an epidemiological survey including 8,387 individuals, cancer patients had the highest depression hazard ratio following the initial two years compared to people diagnosed with other diseases such as diabetes, hypertension, or stroke (23). In addition, the vulnerable groups who experienced significant psychological trauma were more susceptible to developing depressive episodes after cancer diagnosis (24). Interestingly, mental symptoms may appear before cancer in some patients. For example, pancreatic cancer patients suffered fatigue, anorexia, or insomnia for several months before the cancer diagnosis (25). A similar finding was reported in breast cancer, depressive symptoms have been detected in approximately 30% of women before the cancer diagnosis (26). Likewise, both invasive and early-stage ovarian cancer patients presented fatigue and weight loss for 2-7 months before diagnosis (27). In a case-control pilot study, malignant primitive brain tumors (MPBT) risk was significantly linked to major life events over the past 5 years before diagnosis, which indicated that psychological stress might contribute to MPBT appearance (28). Summarily, these results highlight that repetitive stress enables a permissive environment for primary cancer initiation, while tumorigenesis mechanisms may drive mental disorders.

After initial cancer diagnosis, stress levels will decline as a result of adaptive adjustments but reach peaks again during treatment and recurrence (9, 29, 30). In the process of cancer development, stress and affective disorders may accelerate cancer growth and metastasis (31–33). It is now quite clear that the presence of comorbid depression influences most hallmarks of cancer mediated by specific mechanisms including apoptosis resistance, vascularization, epithelial-mesenchymal transition (EMT) and evasion of immune destruction (7, 34). In 2008, a comprehensive meta-analysis was performed to assess the longitudinal associations between psychosocial stress and cancer outcomes (6). The results of this...
study indicated stress-related variables including stress-prone personality, emotional distress and depression had an adverse effect on cancer incidence and survival, despite publication bias existed. Another meta-analysis conducted in 16 prospective cohort studies initiated from 1994 to 2008 found that psychological distress was related to greater cancer mortality, especially in prostate and colorectal cancer (35). Among women with breast cancer, social stress was a critical driver of high mortality (36). Chronic stress also affects central nervous system tumors. For instance, sixty-one percent of the long-term brain cancer survivors experienced elevated stress levels despite their stable disease and less cancer-related concern (37). Of note, brain tumor patients may be reported with higher stress levels than other cancer populations because of the presence of cognitive and neuropsychiatric sequelae.

In addition to psychological elements, many physical factors are also involved in stress-related-tumor development, which are mainly reflected in the course of anti-tumor treatment (9). During perioperative period, patients are more likely to undertake the shedding risk of tumor cells (38, 39). Specifically, this unfavorable physical condition is a result from elevated inflammation responses and stress level originating from tissue damage, wound pain, hypothermia, and specific anesthesia. Another crucial time frame is adjuvant treatment. Despite their powerful tumor killing capacity, adjuvant therapies are always accompanied with side effects such as nausea, diarrhea or insomnia, which are also important components of stressors (40–42). Furthermore, the application of some chemotherapy drugs, like cisplatin and paclitaxel, can activate the inflammation stress pathway and induce various pro-tumorigenic factors expression to facilitate tumor development (43).

Taken together, stress presents in all the stages of tumor. Chronic exposure to multiple stressors increases the susceptibility to cancers, and psychosomatic disorders during survivorship can also contribute to elevated mortality.

**The interaction of stress, neuroendocrine and immunity in cancer**

**Regulation of stress-related hormones in cancer**

The HPA axis and SNS are involved in stress-activated neuroendocrine system (1, 9). Chronic stress stimulates corticotropin-releasing hormone (CRH) release from the hypothalamus and adrenocorticotropic hormone (ACTH) secretion from the pituitary gland, then ACTH triggers the adrenal gland cortex to release cortisol into blood. Catecholamine (epinephrine, norepinephrine and dopamine) is produced from both the adrenal gland medulla and nerve fiber endings (4, 8, 44). All of these stress-related hormones play biological roles through binding to corresponding receptors distributed on the surface of diverse types of cells (Figure 1).

Previous studies have revealed that catecholamine and glucocorticoid promoted tumor initiation and metastasis, which were related to poor survival (31, 45, 46). Consistently, the activation of ARs and GRs signaling pathways could accelerate cancer progression under stress conditions (2, 9, 47). Indeed, the tumor-promoting effects of catecholamine are primarily mediated by the β2 adrenergic receptor (ADRB2) (48, 49). In breast cancer, chronic stress-induced epinephrine release enhanced LDHA-dependent glycolysis to promote stem-like properties of cancer cells (50). Additionally, adrenergic receptor β2 activation by stress-induced epinephrine could promote breast cancer progression through M2 polarization in tumor microenvironment (51). In prostate cancer mice model, researchers revealed that epinephrine activated the ADRB2/PKA/BAD pathway to accelerate cancer development and inhibit chemotherapy-related apoptosis under behavioral stress conditions (10). Similar findings were reported in gastric cancer, exposure to epinephrine altered neuroendocrine phenotypes of tumor cells, leading to invasion and metastasis via the β2-AR/MACCI/axis (31).

Norepinephrine is mainly produced from the adrenal gland cortex, and partly comes from nerve fiber endings. Several in vivo animal studies have assessed its effects on tumor progression. For example, chronic stress elevated norepinephrine levels, which then activated β2-adrenergic receptors and significantly inhibited the PPARγ expression to promote VEGF/FGF2-mediated breast cancer angiogenesis (52). Besides, stress-induced catecholamine activation facilitated M2 macrophage differentiation and induced a metastasis switch in the primary breast cancer mouse model (53). In ovarian carcinoma patients, social isolation promoted norepinephrine secretion, which was correlated with higher malignancies (46). The animal study also suggested that chronic stress stimulated norepinephrine release, resulting in FoxS8 and IL-8-driven ovarian cancer growth (54). Moreover, norepinephrine contributed to the malignant transformation of normal tissues. After chronic unpredictable stress treatment, norepinephrine increased VDCC phosphorylation through ADRB/PKA pathway to facilitate lung epithelial cell malignant transformation and lung tumorigenesis (11).

Glucocorticoid (GC), an extremely critical regulatory molecule in the body, plays roles in growth, development, metabolism and immune regulation (55). In a rodent model, pretreatment with the anxiolytic drug chloridiazepoxide prevented the suppressive effects of psychological stress on innate IFN-gamma production through attenuating the stress-induced corticosterone concentrations (56). In addition, endogenous glucocorticoid assisted the transformation of immunosuppressive phenotype (PD-1+, TIM-3+, Lag3+) in CD8+ T cells (57). In hepatocellular carcinoma, high levels of
GC during depression promoted progression by PD-1 upregulation in tumor-infiltrating natural killer (NK) cells (58). Social defeat elevated plasma corticosterone, as well as induced the expression of glucocorticoid-inducible factor Tsc22d3, which blocked dendritic cells (DCs) and T cell activation to weaken the immunotherapy (12). In addition to immune regulation function, chronic restraint-related glucocorticoid concentration could attenuate p53 function and promote tumorigenesis of colorectal cancer and breast cancer (59).

There are also several hormones participating in stress-mediated changes besides catecholamine and glucocorticoid. As a precursor of epinephrine and norepinephrine, dopamine inhibits tumor growth through the activation of different receptors (60, 61). For example, dopamine treatment blocked stress-induced angiogenesis and tumor growth in ovarian cancer (60). Likewise, chronic stress-mediated vascular growth in ovarian cancer models was prevented by activating the pericyte DR1/cAMP/PKA signaling pathway. Oxytocin (OXT) is a neurohormone released from the hypothalamus (61). Under chronic stress conditions, elevated oxytocin activated the ERK-VEGF/MMP-2 axis to promote lung metastasis of melanoma (62). Besides, Frick et al. (63) found that thyroid hormone levels were reduced under chronic stress, and lymphoma growth was altered. In a rat model, chronic stress could increase prolactin release to facilitate breast cancer, which was blocked by opioid receptor antagonist naltrexone (64).
The studies outlined in this section support that chronic stress alters neuroendocrine homeostasis to facilitate tumor progression, and some classic stress hormones can act as specific clinical biomarkers to evaluate cancer risk. Moreover, it is important to further explore more hormones involved in cancer stress, as well as investigate their mutual regulatory networks (65).

### Neuroendocrine regulation of tumor-associated immune cells

Given ARs and GRs are widely distributed on the surface of immune cells and sympathetic fibers innervate lymphoid organs and tissues, it is easy to conclude that there are interactions between neurons and immune system (49, 66, 67). According to the origin, tumor-associated immune cells are divided into myeloid and lymphocytes to participate in innate and adaptive immunity after maturity. In general, chronic stress suppresses immunogenic cell death embodied in impaired immune-supportive function and increased exhausted immune cells (34). These effects have been summarized in Table 1.

As the first step in adaptive immune priming, DCs play a critical role in antigen presentation (86). Adrenergic stimulation of DCs suppressed their migration through β2-ARs-mediated modulation of interleukin production (87). Similarly, dexamethasone prevented DCs from undergoing maturation and priming T cells efficiently (88). In breast cancer, cold stress influenced phenotypes of DCs in both naïve and tumor-bearing mice (89). After exposure to social disruption, the full maturation and antigen uptake capacity of migratory and lymphoid-resident DCs were impaired, resulting in immunotherapy failure in a mouse model of melanoma (79).

NK cells are essential for innate immune surveillance and subsequent host defense against virus infection or cancer cells (90). NK cell function could be destroyed under different stress conditions. For instance, acute swim stress and epinephrine administration suppressed NK cell activity in rats (91). In hepatocellular carcinoma mice, depression upregulated the PD-1 expression in tumor-infiltrating NK cells and weakened

| Cancer type            | Stressor                        | Target                      | Effects                          | Ref    |
|------------------------|---------------------------------|-----------------------------|----------------------------------|--------|
| Breast Cancer          | Operative stress                | MDSCs                       | Metastasis                       | (68)   |
| Social isolation       | TAMS                            | Tumor growth                |                                  | (51)   |
| Cold stress            | MDSCs                           | Tumor growth                |                                  | (69)   |
| Cold stress            | CTLs, Tregs                     | Immunotherapy failure       |                                  | (70)   |
| Cold stress            | CD8+ T cells                    | Metastasis                  |                                  | (71)   |
| Restraint stress       | Macrophages                     | Metastasis                  |                                  | (53)   |
| Restraint stress       | CD8+ T cells                    | Angiogenesis                |                                  | (72)   |
| Ovarian Cancer         | Restriction stress              | Macrophages                 | Tumor growth                     | (73)   |
| Restriction stress     | Macrophages                     | Tumor growth                |                                  | (74)   |
| Restriction stress     | Macrophages                     | Metastasis                  |                                  | (75)   |
| Colon Cancer           | Social defeat                   | DCs, IHN-7γ T cells         | Immunotherapy failure            | (12)   |
| Cold stress            | CTLs                            | Tumor growth                |                                  | (76)   |
| Scream sound stress    | Th1, Th2                        | Tumor growth                |                                  | (77)   |
| Wet cage exposure      | NK cells                        | Treatment failure           |                                  | (78)   |
| Melanoma               | Social disruption               | DCs, CTLs                   | Immunotherapy failure            | (79)   |
| Cold stress            | CTLs                            | Tumor growth                |                                  | (76)   |
| Wet cage exposure      | NK cells                        | Treatment failure           |                                  | (78)   |
| Squamous cell carcinoma| Restriction stress              | Tregs                       | Tumor growth                     | (80)   |
| Anxiety                | CTLs, Tregs                     | Tumor growth                |                                  | (81)   |
| Lung cancer            | Social defeat                   | DCs, IHN-7γ T cells         | Immunotherapy failure            | (12)   |
| Restriction stress     | Macrophages                     | Lymph vasculature dissemination|                              | (82)   |
| Hepatocellular carcinoma| Restriction stress              | Myeloid cells               | Tumor growth                     | (83)   |
| Prostate Cancer        | Chronic unpredictable mild stress| TAMs                        | Tumor growth                     | (84)   |
| Fibrosarcoma           | Chronic subordinate colony housing| MDSCs, Tregs                | Tumor growth                     | (85)   |
| Lymphoma               | Restriction stress              | CD4+ T cells                | Tumor growth                     | (63)   |
their cytotoxicity (58). Similarly, surgery stress markedly decreased natural killer cytotoxicity (NKCC) through limiting FasL and CD11a expression (92). In breast cancer patients, higher stress levels were associated with decreased IFN-γ production and impaired NKCC (93, 94).

T lymphocytes mediate adaptive immune response and serve as a defender in anti-tumor killing immunity (95). Chronic stress alters the numbers of immune-supportive T cells (CD8+T) and immunosuppressive T cells (Treg), as well as the distribution of helper T (Th) cells-originated cytokines (15). Endogenous glucocorticoid originating from tumor monocyte-macrophage lineage cells could induce exhausted CD8+ T cell phenotype (Tim3+,PD1+) to reduce immune checkpoint blockade efficacy (57). In an anti-cervical cancer mouse model, propranolol strongly improved the STxB7 vaccine efficacy by enhancing the frequency of CD8+ T infiltrating lymphocytes (TILs) (96). Additionally, chronic stress-activated β-AR signaling in tumor-bearing mice impaired the metabolism and function of TILs (76). As mentioned above, DC immaturity also affected subsequent recognition of tumor-associated antigens in cytotoxic T lymphocytes.

Other types of immune cells could also be influenced by chronic stress. For example, β2AR activation in CD4+Foxp3+ T cells led to cAMP/PKA-dependent CREB phosphorylation and enhanced suppressive activity of Treg cells (97). In fibrosarcoma-bearing mice, psychosocial stress accelerated tumor growth through clustering Treg cells and myeloid-derived suppressor cells (MDSCs) in tumor tissues (85). Correspondingly, high-anxious mice showed faster UVB-induced squamous cell carcinoma growth accompanied by increased Treg cells and lower tumor infiltrating cytotoxic lymphocytes (CTLs) infiltration (81). Tumor-associated macrophages (TAMs) are also important components of TME. Prostate cancer patients with depression showed higher scores of CD68+ TAMs infiltration. And in mouse model, chronic stress predominantly promoted MDSCs mobilization and TAMs infiltration to facilitate tumor growth (84). Interestingly, the analysis of tumor specimens from socially isolated breast cancer patients indicated upregulated epithelial-mesenchymal transition gene expression profiles and elevated M2 polarization (98).

In this section, we establish a comprehensive understanding of the interaction between stress and tumor-related immune cells, which is likely to drive novel insights into anti-immunotherapy administration. However, how chronic stress influences other immune cells (e.g., B lymphocytes, cancer-associated fibroblasts), as well as their communication mode in stressful TME remains to be explored.

The mechanisms in the stress-immune-cancer axis

The potential mechanisms of stress induced immunosuppressive TME have been widely investigated (34, 66). Long-term exposure to stressors leads to the concentration of classical catecholamine and glucocorticoid, which are recognized by receptors distributed on immune cells’ surface to reshape the immune microenvironment, and ultimately, drive tumor initiation and progression. Immune responses are divided into three functional categories: inflammation, immune protection, and immune suppression. Here we perform an integrative interpretation and discussion about immune dysregulation mechanisms from these three aspects (Figure 2).

**Inflammatory activation in cancer**

Inflammatory immune responses (IIRs) are adaptive reaction of immune cells to changes in internal and external environment. Moderate IIRs protect the body from pathological damage, while overactivation causes damage (99). It is well known that inflammation contributes to tumor development through oxidative stress damage, DNA mutation and cytokines release. Moreover, there are some tumor initiation-related chronic inflammations such as ulcerative colitis and chronic gastritis, suggesting the strong link between inflammation and cancer (100, 101).

Chronic stress induces sustained elevation in the NF-κB signaling pathway and circulating pro-inflammatory factors (e.g., IL-1β, IL-6, IL-8, TNF-α) to contribute to immune disorders. As we previously reported, gastric adenocarcinoma patients with depression exhibited upregulated oxidative stress states and inflammation responses. In animal model, reactive oxygen species (ROS) was involved in the development of gastric cancer-related depression through inflammation (102).

Likewise, stress-induced sympathetic nervous activation promoted tumor invasion via increasing pro-tumor growth cytokines (e.g., MMP-2, MMP-9, VEGF) (103). Studies documented higher peripheral levels of pro-inflammatory cytokines in mental disorder patients than healthy controls (104, 105). Within 4-8 weeks after surgical resection, the breast cancer patients with depressive symptoms showed greater serum TNF-α, IL-1β, and IL-6 levels (106). Correspondingly, higher IL-6 levels in breast cancer patients were associated with major depressive disorder (107). The whole genome transcriptional profiling identified depressive symptoms had potential links to dysregulation inflammatory biology in metastatic renal cell carcinoma (108). In an animal study, stress elevated the expression of inflammatory cyclooxygenase-2 (COX2), which was required for following lymphatic remodel and tumor dissemination mediated by VEGF-C (82). Similar results were remarkably revealed in patients with ovarian cancer. The patients who lacked social support and experienced worse depression showed higher MMP-9 expression in TAMs (109). Besides, exosome analysis of ovarian cancer patients with lower social support exhibited activated inflammation and mesenchymal polarization (110).
Chronic stress also contributes to cancer-related psychiatric symptoms (19). The pro-inflammatory cytokines produced in the periphery can permeate the blood-brain barrier to impair cognitive processing. For instance, repeated social defeat significantly increased the trafficking of macrophages to brain and inflammatory markers expression on microglia, which led to anxiety-like behavior (111). Thus, the cross-talk along CNS and systematic inflammation is largely responsible for anxiety-like and depression-like behaviors, meanwhile, contributes to carcinogenesis (112).

**Imbalance of protective and suppressive immune responses in cancer**

Tumorigenesis is characterized by immune escape, and immunosurveillance is essential for effective antitumor therapies. Protective immunity is a rapid-activated response to eliminate infections, eradicate tumor cells and intensify vaccine effectiveness including both innate and adaptive immune (66, 113). The alterations in epigenetics and growth dynamics of tumor cells lead to the extracellular secretion of various cytokines that recruit suppressive immune cells (Tregs, MDSCs, TAMs) which are in favor of tumor growth (114).

Chronic stress inhibits protective immunity (113). For example, norepinephrine treatment elevated ADRB2 expression and inflammatory chemokines release in memory CD8+T cells but reduced their proliferation (115). Besides, corticosteroids inhibited DCs maturation leading to blocked Th1 immune responses (88). In clinical studies, the early-stage breast cancer patients with depression produced more Th1 cytokines (IL-12 and IFN-γ), while lower Th1 cytokines (IL-2) and NKCC (57, 97). Similarly, physiologic stress after surgical resection inhibited NKCC and T-cell responses of breast cancer patients (116). In patients with ovarian cancer, depression suppressed the cytotoxicity of NK cells and TILs, while social support alleviated these negative effects (17, 18, 117). More importantly, numerous animal models have been established to observe the effects of stress on tumor immunity. Chronic scream exposure induced freezing behavior in mice and caused a shift from the Th1 to the Th2 responses which significantly promoted cancer progression (77). When exposed to UV radiation, stressed mice had a shorter time to form skin tumors and showed lower IFN-γ, CCL27/CTACK expression.
levels and fewer CD4+ infiltrating cells than control group (80, 81). In terms of distant metastasis, the operative stress increased MDSCs infiltration in the breast cancer microenvironment to assist the EMT process through TGF-β1, VEGF, and IL-10 secretion, finally leading to pulmonary metastases (68). Additionally, chronic unpredictable stress markedly decorated a pre-metastatic niche through increasing the infiltration of macrophages into lung to promote metastatic colonization by tumor cells (32).

The distributions and functions of immune cells are essential for the success of anti-cancer immunotherapy (118). Any therapeutic strategies based on the immune system can be impaired by chronic stress. For instance, social disturbance stress prevented DCs from undergoing full maturation upon antigen uptake and priming CD8+ T cells-mediated cytotoxicity, which finally impaired the effectiveness of vaccines in a murine melanoma model (79). A recent study suggested stress-induced Tsc22d3 expression is a glucocorticoid-inducible factor, which was sufficient to impair DCs function and IFN-γ+ T cell activation, ultimately weakened anti-PD-1 therapy in fibrosarcoma mice (12).

Other potential biological mechanisms

Detecting the mechanisms of stress-induced immunity change in cancer is becoming a hot topic (66, 113). As important responding organs to deliver multiply signals derived from internal and external environment, the brain and gastrointestinal (GI) tract are connected by a bidirectional signaling network called gut-brain axis (119–121). The intestinal microbiota is a critical regulator during gut-brain communication process, and participate in psychological disorders. For example, patients with major depressive disorders had increased levels of Enterobacteriaceae and Alistipes but reduced levels of Faecalibacterium when compared to healthy people (122). Chronic stress can influence microbiota distribution and increase gut permeability. A recent study reported that rats which were more vulnerable to social defeat showed increased expression of immune-modulating microbe such as Clostridia. And when naive rats were treated with microbiota from depression rats, they showed higher microglial density and IL-1β expression (123). In another animal research, chronic restraint stress affected Fimbicutes/Bacteroidetes ratio through Inflammasome-mediated caspase-1 activation to accelerate anxiety symptoms and depressive-like behaviors (124). There are also connections between intestinal microbiota and cancer immunity (125, 126). Enterotoxigenic Bacteroides fragilis (ETBF) promoted tumorigenesis through an IL-17-driven MDSCs generation (127). In colon cancer patients, Fusobacterium nucleatum positivity was significantly associated with microsatellite instability (MSI)-high status and impaired adaptive immunity mediated by T cells (128). Furthermore, altering commensal gut bacteria has been implicated to weaken the effects of tumor immunotherapy (125, 129, 130). In light of this, several researches have been implied to explore the role of gut microbiome in stress-related tumor progression. Cui et al. (131) reported chronic restrained treatment altered mice gut microbiome composition and promoted breast cancer development. However, this field is in its nascency, and specific mechanisms of gut dysbiosis-related tumor progression in stress condition remain unclear.

In addition, inflammatory cytokines led to neuroendocrine cycle dysregulation and severe sleep disorders which were related to poor clinical outcomes in metastatic colorectal cancer and breast cancer patients (2, 19, 132). Metabolic stability is the basis of physiological functions in all organisms. Since immune activation is also an energy-consuming process, it is feasible to explore the relationship between metabolism and immunity under stress conditions. A recent study has indicated physical stress-induced leukotriene B4 triggered severe purine metabolic disorders in CD4+ T cells, which further led to a variety of anxiety-like behaviors in mice (133).

Stress management and anti-cancer treatments

A significant proportion of cancer patients are burdened with varying degrees of chronic stress and this is likely to exert deleterious effects on clinical prognosis (7). It has been reported that appropriate stress modification was efficient to psychological adaptation and favorable clinical outcomes, which provided feasibility to combining stress management and anti-cancer approaches (2, 9).

Blockages of stress-induced hormones

Hormones blockage is an efficient stress manage strategy. Researchers have confirmed the anti-tumor effects of adrenergic receptor antagonists, especially β-ARs antagonists (7, 134, 135). For example, propranolol treatment and β2-AR knockout decreased exhausted T cells infiltration and inhibited melanoma growth in mice (76). Low-dose β-ARs blocker (propranolol) therapy reduced MDSCs accumulation and relieved thermal stress-induced breast cancer growth (69). Besides, propranolol enhanced the sensitivity of gastric cancer cells to radiation through the NF-κB-VEGF/EGFR/COX-2 pathway (136). Ablation of the sympathetic nerve and β-adrenergic signaling blockage significantly inhibited stress-induced lung colonization of tumor cells (32). Furthermore, combined administration of propranolol and chemotherapy could improve the life quality of epithelial ovarian cancer patients (137). In a nested case-control study containing 4113
pancreatic patients, the individuals who used selective β1-blockers or non-selective β-blockers had lower cancer risk (138). IC1118,551, a specific ADRB2 antagonist, suppressed gastric cancer metastasis via inhibiting the ERK1/2-JNK-MAPK pathway (139). Similar results were also demonstrated in hepatic and pancreatic cancer (33, 140).

In addition to common adrenergic inhibitors, many antioxidants also showed anti-tumor activity. As but one example, melatonin remarkably reduced the abdominal metastasis of ovarian cancer induced by chronic restraint stress, and this impact was partially mediated by the inhibition of the NE/AKT/β-catenin/Slug axis (75). Considering the role of stress in immune regulation, hormone blockers may be ideal partners for immunotherapy. For instance, propranolol strongly increased the density and PD-1 expression of CTLs, which promoted the anti-tumor toxicity of STxBE7 vaccine in rodent models (96). Similarly, mifepristone administration reversed the negative impact of stress, as well as facilitated prophylactic immunotherapy effectiveness in socially defeated mice (56).

Summarily, the beneficial effects of propranolol have been demonstrated in many clinical researches (3, 137, 141, 142), and there are also two randomized controlled trials (RCTs) that initially combined propranolol and etodolac (COX-2 inhibitor) in breast and colorectal cancer (143, 144). All of these clinical findings have proved the application of β-ARs antagonists was a promising strategy to manage stress in cancer patients.

Psychosomatic behavior management

Psychosomatic symptoms intervention suggests a novel therapeutic strategy for cancer patients experiencing chronic stress (66). Cognitive behavior treatment (CBT) is a kind of psychotherapy approach aimed to restructure patients’ cognition. The non-metastatic breast cancer patients who participated in cognitive intervention had a well-maintained decreased cortisol levels and improved relaxation ability (109).

In another RCT of breast cancer, women in the CBT-based stress management group showed decreased emotional distress, upregulation in cellular immunity and better health condition in comparison with the control group (145, 146). In addition, previous studies revealed that mindfulness-based approaches exhibited strong capacity in relieving cancer-related stress (147). For example, mindfulness intervention provided metastatic cancer patients with an opportunity for pain control and spiritual relief, which possibly reinforced the effectiveness of early palliative care (148). Moreover, the brain’s reward system activation attenuated SNS-mediated MDSCs development in bone marrow, followed by less immunosuppressive and tumor growth inhibition in a murine model (149).

Considering the psychological damage in cancer patients, researchers have found that enriched living environment and social support were helpful to improve overall life quality (2). For example, when mice were housed in an enriched environment, they displayed enhanced NK cell immunity and retardative tumor malignancies (150). Besides, the enriched environment activated peripheral SNS/β-ARs/CCL2 signaling pathway, which protected mice from liver neoplasia growth and PD-L1 treatment resistance through increasing CD8+ T cells cytotoxic effect (151). In a study about community life support programs, the cancer patients experienced better quality of life after volunteer-provided palliative (152). The potential of dietary strategies in influencing carcinogenesis has been well established in epidemiological researches (19). Mediterranean diet, characterized by a higher intake proportion of monounsaturated, fruits and vegetable intake, is related to plasma stress-induced cortisol expression in adolescents (153). Furthermore, fatigue reduction diet for breast cancer patients contributes to improvements in sleep quality and fatigue symptoms (154).

Since moderate physical exercise plays a vital role in modulating neuroendocrine activity and strengthening immunosurveillance, researchers have tried to explore the influences of exercise on psychosomatic function in cancer survivors. Compared to control group, the individuals with hematological cancers who underwent an adjunctive exercise program during treatment were reported with less physical fatigue and greater physical function (155). Similar results were indicated in solid tumors, a 12-week exercise program could reduce anxiety and depression in lung cancer and prostate cancer patients (156, 157). Moreover, as a kind of new-style sport, yoga was an efficacious way to relieve cancer-related depression and improve sleep disturbance among cancer survivors (158–160). Additionally, other physical stress interventions including massage, Tai-Chi, and Chinese acupuncture have been also tested in cancer treatment (2, 66).

Although psychosomatic interventions have shown promising results in anti-cancer treatment, there was still insufficient evidence to support its clinical application. In a comprehensive review, the authors summarized 22 RCTs about psychosocial stress-reducing strategies, and they pointed out that most intervention did not significantly improve long-term cancer outcomes. Additionally, some of these studies had been criticized for methodological deficiencies (9). Hence, the administration of psychosomatic management strategies in cancer treatment should be more carefully explored.

Anti-depressants application

The idea of anti-depressants application in cancer treatment is highly controversial. In animal studies, fluoxetine treatment after melanoma cells injection inhibited tumor growth, whereas chronic pre-treatment with fluoxetine before melanoma bearing accelerated metastasis formation through impairing protective
immune responses (161, 162). Inconsistent results were also found in clinical practice (163, 164). In a double-blind trial, fluoxetine treatment was well tolerated in advanced cancer patients and showed prevalent effectiveness in anxiety and depression reduction (165). Some anti-depressant drugs (e.g., paroxetine) could alleviate the side effects of chemotherapy like nausea and anorexia (19). Nevertheless, long-term intake of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) might increase the risk of breast and ovarian cancer (166, 167). In a RCT enrolled 189 patients with advanced cancer, sertraline did not exert significant improvement in symptoms and survivorship (168). Collectively, the effects of anti-depressants on cancer populations are largely unclear and more researches are needed to fully evaluate their impact on long-term outcomes.

Conclusion and perspectives

It is widely accepted that stress exposure creates negative influences on most hallmarks of cancer to facilitate tumorigenesis and progression. Meanwhile, cancer patients are vulnerable to psychosomatic disorders (e.g., insomnia, anxiety and depression), which are also major sources of chronic stress (7, 34, 66). The underlying molecular mechanisms have been identified in numerous pre-clinical studies, and we concluded the interaction of stress, neuroendocrine and cancer immune systems in this review. In general, chronic stress exerts positive effects on the HPA axis and SNS activation, which finally results in inflammation upregulation and suppressive cellular immunity toxicity. Under the mediation of multiple cytokines, immune cells communicate with circulating cancer cells in TME to promote tumor growth, angiogenesis and metastasis.

Given the close link between stress and cancer, the importance and effectiveness of stress management have been stated (2, 9). However, there are still some technological controversies in animal models and methodological deficiencies in clinical trials, as discussed below. 1) Although most preclinical studies show satisfactory results, some studies reach unexpected conclusions. For example, in a social isolation mice model, chronic stress suppressed mammary tumor growth through β-Adrenergic signaling (169). These contrary results are partly attributed to the subtle discrepancy of different stressors exposure (e.g., restraint stress, cold stress and social defeat). Approximately 30–40 percent of mice showed a resilient phenotype after social defeat (170), which meant the duration and intensity of stress exposure were critical. The detection of pre-existing stress levels in mice before modeling is also a critical problem that we usually ignore (34, 171). In addition, it is necessary to construct appropriate animal models according to purposes. When the stressors exposure predate tumor injection, researchers focus on the cancer susceptibility in the individuals experienced chronic stress, while the opposite condition pays attention to comprehensive influence of stress on tumor development (34). Finally, exogenous catecholamine or glucocorticoid treatment is difficult to simulate neuroendocrine changes of the body under stress condition. 2) As we briefly reviewed in last section, clinical stress-reducing interventions yield mixed effects on long-term cancer outcomes. RCTs so far usually use different treatment protocols (e.g., initial time and duration) and these heterogeneities may be the source of inconsistent results (9). Another problem to be aware of is methodological deficiencies. For example, assignment bias might cause the false positive conclusion of psychological interventions (172, 173). Actually, only a few positive outcomes have been replicated for validity because of various practical difficulties in the implementation of clinical trials.

The discrepancy between preclinical and clinical outcomes suggests the following aspects need to be further clarified in future studies. The first question is “who can benefit”. Physical examination and psychological tests play a critical part in this step. For example, the population who are older or psychologically vulnerable may benefit from psychological interventions (174). Importantly, cancer patients with cardiovascular disease should be given more caution when using β-ARs blockages (7). In addition, most of current available clinical evidence focuses on breast cancer and it is still a problem to address understudied populations. The next one is “when to intervene”. The interventions during appropriate phases may bear great effects. Although it is quite difficult to synchronize the critical periods of cancer initiation with stress, perioperative and adjuvant treatment phases during cancer treatment are more sensitive to stress-reducing interventions (9). The last one is “how to intervene”. As growing types of stress management strategies show effects on relieving psychological symptoms, present questions move to how to combine these approaches to improve long-term clinical outcomes in cancer patients. It has been demonstrated that multiple stress management models simultaneously containing relaxation training, cognitive behavior treatment and health education showed promising treatment capacity (66). The internet-based remote management programs also effectively improve the quality of life of cancer patients (175). Of note, it is still an unexplored field about the combined application of immunotherapy and psychological interventions in cancer treatment.

In conclusion, we provide a wide insight into the multiple interactive biobehavioral molecular pathways linking stress, immunity and cancer. Despite the absence of unified stress measurement tools and specific efficacy evaluation criteria makes stress difficult to explore, personalized stress management based on different pharmacological and psychosocial approaches will become an important component of tumor precision therapy in the future.

Author contributions

YW developed the concept and design. YLiu and ST wrote the manuscript. BN, TH, and YLi provided critical discussion and edited the manuscript. All authors listed have made a
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References

1. Krizanova O, Babula P, Pacak K. Stress, catecholaminergic system and cancer. Stress (2016) 19(4):419–28. doi: 10.1080/10253890.2016.1203415
2. Cui B, Peng F, Lu JX, He B, Su QT, Luo HD, et al. Cancer and stress: NextGen strategies. Brain Behav Immun (2021) 93:368–83. doi: 10.1016/j.bbi.2020.11.005
3. Dai SR, Mo YZ, Wang YM, Xiang B, Liao QJ, Zhou M, et al. Chronic stress promotes cancer development. Front Oncol (2020) 10. doi: 10.3389/fonc.2020.01492
4. Russell G, Lightman S. The human stress response. Nat Endocrinol (2019) 15(9):525–34. doi: 10.1038/s41556-018-0222-0
5. O’Connor DB, Thayer JF, Vedhara K. Stress and health: A review of psychobiological processes. Ann Rev Psychol (2021) 72:663–88. doi: 10.1146/annurev-psych-062520-122331
6. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol (2008) 5(8):466–75. doi: 10.1038/ncponc.1134
7. Hong H, Ji M, Lai D. Chronic stress effects on tumor: Pathway and mechanism. Front Oncol (2021) 11:738252. doi: 10.3389/fonc.2021.738252
8. Falcinelli M, Thaker PH, Lutgendorf SK, Conzen SD, Flaherty RL, Flint MS. The role of psychologic stress in cancer initiation: Clinical relevance and potential molecular mechanisms. Cancer Res (2021) 81(20):3131–40. doi: 10.1158/0008-5472.CAN-21-0684
9. Ekerling A, Ricon Becker I, Soroki L, Sandbank E, Ben-Elyahu S. Stress and cancer: mechanisms, significance and future directions. Nat Rev Cancer (2021) 21(12):767–85. doi: 10.1038/s41562-021-00395-5
10. Hassan S, Karpova Y, Baiz D, Yancey D, Pullikuth A, Flores A, et al. Behavioral stress accelerates prostate cancer development in mice. J Clin Invest (2013) 123(2):874–86. doi: 10.1172/JCI63324
11. Jang HJ, Boo HJ, Lee HJ, Min HY, Lee HY. Chronic stress facilitates lung tumorigenesis by promoting exocytosis of IGf2 in lung epithelial cells. Cancer Res (2016) 76(22):6607–19. doi: 10.1158/0008-5472.CAN-16-0990
12. Yang H, Xia L, Chen J, Zhang S, Martin V, Li Q, et al. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. Nat Med (2019) 25(9):1428–41. doi: 10.1038/s41591-019-0566-4
13. Obradovic MMS, Hamelin B, Manevski N, Couto JP, Sethi A, Coissieux MM, et al. Glucocorticoids promote breast cancer metastasis. Nature (2019) 567(7749):540–4. doi: 10.1038/s41586-019-1019-4
14. Pan D, Kocherginsky M, Conzen SD. Activation of the glucocorticoid receptor is associated with poor prognosis in estrogen receptor-negative breast cancer. Cancer Res (2011) 71(20):6360–70. doi: 10.1158/0008-5472.CAN-11-0362
15. Colon-Echevarria CR, Lamboy-Caraballo R, Aquino-Acevedo AN, Armaiz-Pena GN. Neuroendocrine regulation of tumor-associated immune cells. Front Oncol (2019) 9:1077. doi: 10.3389/fonc.2019.01077
16. Sephton SE, Dhbabh F, Keuroghlian AS, Giese-Davis J, McEwen BS, Ionan AC, et al. Depression, cortisol, and suppressed cell-mediated immunity in metastatic breast cancer. Brain Behav Immun (2009) 23(8):1148–55. doi: 10.1016/j.bbi.2009.07.007
17. Lutgendorf SK, Sood AK, Anderson B, McGinn S, Maiseri H, Dao M, et al. Social support, psychological distress, and natural killer cell activity in ovarian cancer. J Clin Oncol (2005) 23(20):7105–13. doi: 10.1200/JCO.2005.10.015
18. Lamkin DM, Lutgendorf SK, McGinn S, Dao M, Maiseri H, DeGeest K, et al. Positive psychosocial factors and NKT cells in ovarian cancer patients. Brain Behav Immun (2008) 22(1):65–73. doi: 10.1016/j.bbi.2007.06.005
19. Bortolato B, Hphyantis TN, Valpione S, Perini G, Maes M, Morris G, et al. Depression in cancer: The many biobehavioral pathways driving tumor progression. Cancer Treat Rev (2017) 52:58–70. doi: 10.1016/j.ctrv.2016.11.004
20. Cardoso G, Graa J, Khrt C, Trancas B, Papola A. Depression and anxiety symptoms following cancer diagnosis: a cross-sectional study. Psychol Health Med (2016) 21(5):562–70. doi: 10.1080/13548506.2015.1225006
21. Gil F, Costa G, Hilker I, Benito L. First anxiety, afterwards depression: Psychological distress in cancer patients at diagnosis and after medical treatment. Stress Health (2012) 28(5):362–7. doi: 10.1002/smi.2445
22. Carlson L. High levels of untreated distress and fatigue in cancer patients. Psycho-Oncol (2004) 13(8):737–49. doi: 10.1002/pon.8187
23. Polsky D, Doshi JA, Marcus S, Olin D, Rothbard A, Thomas N, et al. Long-term risk for depressive symptoms after a medical diagnosis. Arch Intern Med (2005) 165(11):1260–6. doi: 10.1001/archinte.165.11.1260
24. Kangas M, Henny JL, Bryant RA. The course of psychological disorders in the 1st year after diagnosis. J Consult Clin Psychol (2005) 73(4):763–8. doi: 10.1037/0022-006X.73.4.763
25. Green AI, Austin CP. Psychopathology of pancreatic cancer: a psychobiologic probe. Psychosomatics (1993) 34(3):208–21. doi: 10.1016/S0033-3182(93)71882-4
26. Van Esch L, Roukema JA, Ernst MF, Nieuwenhuijzen GAP, De Vries J. Combined anxiety and depressive symptoms before diagnosis of breast cancer. J Affect Disord (2012) 136(3):895–901. doi: 10.1016/j.jad.2011.09.012
27. Vine MF, Calingaert B, Berchuck A, Schaidt KR. Characterization of pre-diagnostic symptoms among primary epithelial ovarian cancer cases and controls. Gynecol Oncol (2003) 90(1):75–82. doi: 10.1016/S0090-8258(03)00175-6
28. Cabaniols C, Giorgi R, Chinot O, Ferahta N, Spinelli V, Alla P, et al. Links between private habits, psychological stress and brain cancer: a case-control pilot study in France. J Neurol Oncol (2011) 103(2):307–16. doi: 10.1007/s11763-010-0386-1
29. Andersen BL, Shapiro CL, Farrar WB, Crespin T, Wells-Degregorio S. Psychological responses to cancer recurrence - a controlled prospective study. Cancer (2005) 104(7):1540–7. doi: 10.1002/cncr.21309
30. Linden W, Vordenmaier A, MacKenzie R, Greig D. Anxiety and depression after cancer diagnosis: Prevalence rates by cancer type, gender, and age. J Affect Disord (2012) 141(2–3):343–51. doi: 10.1016/j.jad.2012.03.025

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use of intraoperative dexmedetomidine is not associated with a reduction in acute reaction during colorectal cancer resection. J Oncol (2017) 3(11):1365–70. doi: 10.1186/s40429-016-0305

38. Yamaguchi K, Takagi Y, Aoki S, Futamura M, Saji S. Significance of increased circulating cancer cells in the blood by reverse transcriptase-polymerase chain reaction during colorectal cancer resection. Ann Surg (2000) 232(1):58–65. doi: 10.1097/00000452-200007000-00009

39. Hashimoto M, Tanaka F, Yoneda K, Takuwa T, Matsumoto S, Okumura Y, et al. Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis. J Neurosci (2007) 27(33):8857–65. doi: 10.1523/JNEUROSCI.1247-07.2007

40. Tejwani GA, Gudeethipu KP, Hanissian SH, Arcos ML, Genaro AM, et al. Involvement of thyroid hormones in the alterations of T-cell immunity and tumor progression induced by chronic stress. Biol Psychiatry (2009) 65(11):935–42. doi: 10.1016/j.biyscpys.2008.12.013

41. Hiro T, Liu N, Li J, Chen D, Luo D, Sun Q, et al. Oxytocin involves in chronic stress-evoked melanoma metastasis via beta-2-adrenergic 2-mediated ERK signaling pathway. Carcinogenesis (2019) 40(11):1395–404. doi: 10.1093/carcin/bgy106

42. Frick LR, Papaneli M, Bussmann UA, Klecha AI, Arcos ML, Genaro AM, et al. Involvement of thyroid hormones in the alterations of T-cell immunity and tumor progression induced by chronic stress. J Neurosci (2007) 27(33):8857–65. doi: 10.1523/JNEUROSCI.1247-07.2007

43. Liu et al. 10.3389/fimmu.2021.801915

44. Luan F, Ju Y, Jiang L, Wang J, Gou W, Zhang C, et al. Circulating tumor cells in pulmonary venous blood lead to the failure of therapy and metastasis. J Cancer Clin Oncol (2012) 30(23):2885–92. doi: 10.1159/000344421

45. Wu WZ, Liu SG, Liang YF, Zhou ZG, Bian W, Liu XQ. Stress hormone cortisol enhances Bcl2-like-12 expression to inhibit p53 in hepatocellular carcinoma cells. Oncotargets Ther (2016) 9:637–41. doi: 10.1016/j.clinthera.2016.05.004

46. MacLarkey WB. Facilitation of dimethylbenz[a]anthracene-induced rat mammary tumorigenesis by restraint stress: role of beta-endorphin, prolactin and naltrexone. Carcinogenesis (1991) 12(4):637–41. doi: 10.1093/carcin/12.4.637

47. Xu Y, Yan J, Tao Y, Qian X, Zhang C, Yin L, et al. Pituitary hormone alpha-MSH promotes tumor-mediated myeloid suppression and immunosuppression. Science (2022) 377(6610):1085–91. doi: 10.1126/science.abd2764

48. Antoni MH, Dhabhar FS. The impact of psychosocial stress and stress management on immune responses in patients with cancer. Cancer (2019) 125(9):1417–31. doi: 10.1002/cncr.31943

49. Sloan EP, Capitanio JP, Tarara RP, Mendoza SP, Mason WA, Cole SW. Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis. J Neurosci (2007) 27(33):8857–65. doi: 10.1523/JNEUROSCI.1247-07.2007

50. Ma X, Wang M, Yin T, Zhao Y, Wei X, Myeloid-derived suppressor cells promote metastasis in breast cancer after the stress of operative removal of the primary cancer. Front Oncol (2019) 9:855. doi: 10.3389/fonc.2019.00855

51. MacDonald G, Minnipro S, Panedy M, Robinson D, Hong EF, Hylander B, et al. Comparing thermal stress reduction strategies that influence MDSC accumulation in tumor bearing mice. Cell Immunol (2021) 361(1):104285. doi: 10.1016/j.cellimm.2021.104285

52. Buseck MJ, Qiao GX, MacDonald CR, Girdharthun TA, Evans L, Niedzwiecki B, et al. Beta-adrenergic signaling in mice housed at standard temperatures suppresses an effector phenotype in CD4(+) T cells and undermines checkpoint inhibitor therapy. Cancer Res (2017) 77(20):5639–51. doi: 10.1158/0008-5472.can-17-0546

53. Kokolus KM, Capitanio ML, Lee CT, Eng JW, Wagh JT, Hylander BL, et al. Baseline tumor growth and immune control in laboratory mice are significantly influenced by subthermoneutral housing temperature. Proc Natl Acad Sci U.S.A. (2013) 110(20):7016–21. doi: 10.1073/pnas.1224911110

54. Budiu RA, Vlad AM, Nazario L, Bathula C, Cooper KL, Edmed J, et al. Restraint stress and mouse isolation stress differentially regulate adaptive immunity and tumor angiogenesis in a breast cancer model. Front Oncol (2017) 7(1):61–12. doi: 10.3389/can.2017.00112

55. Colonial-Echevarria CB, Ortiz T, Maldonado L, Hidalgo-Vargas MJ, Perez-Morales J, Aquino-Acevedo AN, et al. Zoledronic acid abrogates restraint-stress
induced macrophage infiltration, PDGF-AA expression, and ovarian cancer growth. Cancer (2020) 129(9):2671. doi: 10.1002/cncr.332671

74. Armaiz-Pena GN, Gonzalez Villavasna V, Nagaraj A, Rodriguez-Aguayo C, Sadowski NC, Stone RL, et al. Adrenergic regulation of monocyte chemotactic protein 1 leads to enhanced macrophage recruitment and ovarian carcinoma growth. Oncotarget (2015) (5):66)2466–73. doi: 10.18632/oncotarget.2887

75. Bu SX, Wang Q, Sun JY, Li X, Gu TT, Lai DM. Melatonin suppresses chronic restraint stress-mediated metastasis of epithelial ovarian cancer via NR1/ AKBeta-catenin/SLUG axis (vol 56, pg 891, 2020). Cell Death Dis (2020) 11(8):1–17. doi: 10.1038/s41419-020-02958-0

76. Quao G, Chen MH, Mohammadpour H, MacDonald CR, Bucek MJ, Hylander BL, et al. Chronic adrenergic stress contributes to metabolic dysfunction and an exhausted phenotype in T cells in the tumor microenvironment. Cancer Immunol Immunother (2021) 9(6):651–64. doi: 10.1007/s00262-020-02445-0

77. Hou N, Zhang X, Zhao L, Zhao X, Li Z, Song T, et al. A novel chronic stress-induced shift in the Th1 to Th2 response promotes colon cancer growth. Biochem Biophys Res Commun (2013) 439(4):471–6. doi: 10.1016/j.bbrc.2013.08.101

78. Levi B, Matzner P, Goldfarb Y, Soroki L, Shaashua I, Melamed R, et al. Stress impairs the efficacy of immune stimulation by CPG. Potential neuroendocri ne mediating mechanisms and significance to tumor metastasis and the perioperative period. Brain Behav Immun (2016) 56:209–20. doi: 10.1016/j.bbi.2016.02.025

79. Sommershof A, Schueremoen L, Koerner J, Groettrup M. Chronic stress suppresses anti-tumor TCD8+ responses and tumor regression following cancer immunotherapy in a mouse model of melanoma. Biochem Immunol (2017) 65:140–9. doi: 10.1016/j.biim.2017.04.021

80. Saul AN, Obersayyin TM, Daugherty C, Jones S, Jewell S, et al. Chronic stress and susceptibility to skin cancer. J Natl Cancer Inst (2005) 97 (23):1760–7. doi: 10.1093/jnci/dji041

81. Dhabhar FS, Saul AN, Holmes TH, Daugherty C, Neri E, Tille JM, et al. High-anxious individuals show increased chronic stress burden, decreased protective immunity, and increased cancer progression in a mous model of squamous cell carcinoma. PloS One (2012) 7(4):e30336. doi: 10.1371/journal.pone.0030336

82. Le CP, Nowell CJ, Kim-Fuchs C, Botteri E, Hiller JG, Ismail H, et al. Chronic stress and immune system responses in breast cancer patients with high levels of psychological stress is associated with altered expression of killer immunoglobulin-like receptors. J Exp Med (2007) 195(9):1365–44. doi: 10.1084/jem.2006.08.037

83. Von Ah D, Rang DH, Carpenter JS. Stress, optimism, and social support: impact on immune responses in breast cancer. Res Nurs Health (2007) 30(1):72–83. doi: 10.1002/nur.20164

84. Coble PG, Van den Eynde BJ, van der Bruggen P, Boon T. Tumour antigens recognized by T lymphocytes at the core of cancer immunotherapy. Nat Rev Cancer (2014) 14(2):135–46. doi: 10.1038/nrc3670

85. Daher C, Vimeux L, Stoera R, Peranouzzi E, Bismuth G, Wiedwald E, et al. Blockade of beta-adrenergic receptors improves CD8(+) T cell priming and cancer vaccine efficacy. Cancer Immunol Res (2019) 7(11):1849–63. doi: 10.1158/2326-6066.CIR-18-0833

86. Guerreschi MG, Araujo LP, Maricato JT, Takanac MK, Nascimento VM, Vivanco BC, et al. Beta2-adrenergic receptor signaling in CD4+Foxp3+ regulatory T cells enhances their suppressive function in a FCA-dependent manner. Eur J Immunol (2013) 43(4):1001–12. doi: 10.1002/eji.201242805

87. Maestroni GJM, Mazzola P. Langerhans cells beta 2-adrenoceptors: role in inflammation signaling pathway. J Cell Mol Med (2015) 13:585–6. doi: 10.1111/jcmm.12336

88. Matyszak MK, Citterio S, Rescigno M, Ricciardi-Castagnoli P. Differential influences phenotype of T cells in the tumor microenvironment. Front Immunol (2019) 8:1423. doi: 10.3389/fimmu.2019.01423

89. Kokolus KM, Spangler HM, Povinelli BJ, Farren MR, Lee KP, Repasky EA. Beta-adrenergic receptor antagonism prevents anxiety-like behavior and stress: A role for adrenal catecholamines and beta-adrenoceptors. Neuroimmunomodulation (2000) 7(3):154–64. doi: 10.1159/000045276

90. Glasner A, Avraham R, Rosenne E, Bensh M, Zimora O, Shemer S, et al. Improving survival rates in two models of spontaneous postoperative metastasis in mice by combined administration of a beta-adrenergic antagonist and a cytochrome-x2 inhibitor. J Immunol (2010) 184(5):2449–57. doi: 10.4049/ jimmunol.0903301

91. Vazker MA, Terrell CE, Welt M, Suleiman S, Thornton L, Andersen BL, et al. Impaired natural killer cell lysis in breast cancer patients with high levels of metastasis.
Targeting the gut and tumor microbiota in cancer.

In (2020) 25(5):1068

The gut microbiome regulates the increases in depressive-type behaviors and in (2015) 48:186

Frontiers in Immunology frontiersin.org

Liu et al. 10.3389/jimmunol.2018.05.014

Chaudhary KR, Yan SX, Heibronn SP, Sonett JR, Stoopler MB, Shu C, et al. Effects of beta-adrenergic antagonists on chemoradiation therapy for locally advanced non-small cell lung cancer. J Clin Med (2019) 8(3):575. doi: 10.3390/jcm8030575

Spina, et al. Perioperative inhibition of beta-adrenergic and COX2 signaling in a clinical trial in breast cancer patients improves tumor ki-67 expression, serum cytokine levels, and PBMCs transcriptome. Brain Behav Immun (2018) 73:294-309. doi: 10.1016/j.bbi.2018.05.014

Haider R, Ricon-Becker I, Radin A, Gutman M, Cole SW, Zmora O, et al. Perioperative COX2 and beta-adrenergic blockade improves biomarkers of tumor metastasis, immunity, and inflammation in colorectal cancer: A randomized controlled trial. Cancer (2020) 126(17):3991-4001. doi:10.1002/cncr.32950

Andersen BL, Farrar WB, Golden-Kreutz DM, Glaser EM, Crespin TR, et al. Psychological, behavioral, and immune changes after a psychological intervention: A clinical trial. J Clin Oncol (2004) 22(17):3570-80. doi: 10.1200/JCO.2004.06.030

Andersen BL, Farrar WB, Golden-Kreutz DM, Glaser EM, Crespin T, et al. Distress reduction from a psychological intervention contributes to improved health for cancer patients. Brain Behav Immun (2007) 21(7):953-61. doi: 10.1016/j.bbi.2007.03.005

Rouleau CR, Garland SN, Carlsson LE. The impact of mindfulness-based interventions on symptom burden, positive psychological outcomes, and biomarkers in cancer patients. Cancer Manag Res (2015) 7:1211–31. doi: 10.2147/CmrrS.S64165

Polecit S, Razzini G, Ferrari R, Piccirilli MP, Spedicato GA, Pasqualini A, et al. Mindfulness-based stress reduction in early palliative care for people with metastatic cancer: A mixed-method study. Complement Ther Med (2019) 47:102218. doi:10.1016/j.ctim.2019.102218

Ben-Shaanan TL, Schiller M, Arazy-Debby H, Korin B, Boshnak N, Koren T, et al. Modulation of anti-tumor immunity by the brain's reward system. Nat Commun (2018) 9(1):1–10. doi:10.1038/s41467-018-05283-5

Song YF, Gan Y, Wang Q, Meng ZH, Li Korin B, Boshnak N, Koren T, et al. Modulation of anti-tumor immunity by the brain's reward system. Nat Commun (2018) 9(1):1–10. doi:10.1038/s41467-018-05283-5

Liu CB, Yang C, Li L, Li QJ, Wang XN, et al. Environmental eustress modulates beta-Ars/CCL2 axis to induce anti-tumor immunity and sensitive immunotherapy against liver cancer in mice (vol 12, 5725, 2021). Nat Commun (2021) 12(1):1–15. doi:10.1038/s41467-021-26376-8

Walshe C, Preston N, Payne S, Dodd S, Algorta GP. Quality of life trends in women with and without cancer referred to volunteer-provided palliative care services (ELSA): A longitudinal study. J Pain Symptom Manage (2018) 56(3):689-98. doi:10.1016/j.painsymman.2017.08.020

Carvalho KMB, Ronca DB, Michels N, Huybrechts I, Caena-Garcia M, Marcos A, et al. Does the Mediterranean diet protect against stress-induced inflammatory activation in European adolescents? the HELENA study. Nutrients (2018) 10(11):1770. doi:10.3390/nu10111770

Zick SM, Colacino J, Cornellier M, Khairi T, Surnow K, Djuric Z. Fatigue reduction diet in breast cancer survivors: a pilot randomized clinical trial. Breast Cancer Res Tr (2017) 161(2):299–310. doi:10.1007/s12046-016-0470-y

Furzer BJ, Ackland TR, Wallman KE, Pettersson AS, Gordon SM, Wright KE, et al. A randomised controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in haematological cancer patients. Support Care Cancer (2016) 24(4):1697-707. doi:10.1007/s00520-015-2955-7
selective serotonin reuptake inhibitors and survival in newly diagnosed cancer

156. Livingston PM, Craike MJ, Salmon J, Courneya KS, Gaskin CJ, Fraser SF, et al. Effects of a clinician referral and exercise program for men who have completed active treatment for prostate cancer: A multicenter cluster randomized controlled trial (ENGAGE). Cancer (2015) 121(15):2646–54. doi: 10.1002/cncr.29385

157. Chen HM, Tsai CM, Wu YC, Lin KC, Lin CC. Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. Br J Cancer (2015) 112(3):438–45. doi: 10.1038/bjc.2014.612

158. Mizrahi D, Broderick C, Friedlander M, Ryan M, Harrison M, Pumpa K, et al. An exercise intervention during chemotherapy for women with recurrent ovarian cancer: a feasibility study. Int J Gynecol Cancer (2015) 25(6):985–92. doi: 10.1097/IGC.0000000000000460

159. Lin PJ, Klickner IR, Loh KP, Inglis JE, Peppone LJ, Janelins MC, et al. Influence of yoga on cancer-related fatigue and on meditational relationships between changes in cancer and cancer-related fatigue: A nationwide, multicenter randomized controlled trial of yoga in cancer survivors. Int J Cancer Ther (2019) 18:1534775419855134. doi: 10.1177/1534114019855134

160. Rao RM, Raghuram N, Nagendra HR, Usharam MR, Kopinath KS, Dwakar RR, et al. Effects of an integrated yoga program on self-reported depression scores in breast cancer patients undergoing conventional treatment: A randomized controlled trial. Indian J Palliat Care (2015) 21(2):174–81. doi: 10.4103/0973-1075.156486

161. Grygier B, Arteta B, Kubera M, Basta-Kaim A, Budziszewska B, Leskiewicz M, et al. Inhibitory effect of antidepressants on B16F10 melanoma tumor growth. Pharmacol Rep (2013) 65(3):672–81. doi: 10.1016/S1734-1140(13)71045-4

162. Kubera M, Grygier B, Wronta D, Rogoż Z, Roman A, Basta-Kaim A, et al. Stimulatory effect of antidepressant drug pretreatment on progression of B16F10 melanoma in high-active male and female C57BL/6 mice. J Neuroimmunol (2011) 240:34–44. doi: 10.1016/j.jneuroim.2011.09.006

163. Budvytė J, Mılıs K, Zhang SD, Liberante FG, Cardwell CR. Selective serotonin reuptake inhibitor use and breast cancer survival: a population-based cohort study. Breast Cancer Res (2018) 20(1):1–10. doi: 10.1186/s12933-017-0792-0

164. Bourouzi L, Lurie J, Haynes K, Mamtani R, Yang YX. Chronic therapy with selective serotonin reuptake inhibitors and survival in newly diagnosed cancer patients. Eur J Cancer Care (2018) 27(1):e12666. doi: 10.1111/ecc.12666

165. Fisch MJ, Loehrer PJ, Kristeller J, Passik S, Jung SH, Shen ZJ, et al. Fluoxetine versus placebo in advanced cancer outpatients: A double-blinded trial of the Hoosier oncology group. J Clin Oncol (2003) 21(10):1957–43. doi: 10.1200/JCO.2003.08.025

166. Cotterchio M, Kreiger N, Darlington G, Steingart A. Antidepressant medication use and breast cancer risk. Am J Epidemiol (2000) 151(10):951–7. doi: 10.1093/oxfordjournals.aje.a010138

167. Sharpe CR, Collet JP, Belzile E, Hanley JA, Boivin JF. The effects of tricyclic antidepressants on breast cancer risk. Brit J Cancer (2002) 86(1):92–7. doi: 10.1038/sj.bjc.6600033

168. Stockler MR, O’Connell R, Nowak AK, Goldstein D, Turner J, Wicken NR, et al. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. Lancet Oncol (2007) 8(7):603–12. doi: 10.1016/S1470-2045(07)70148-1

169. Dawes RP, Burke KA, Bynu DK, Xu Z, Statka P, Chan L, et al. Chronic stress exposure suppresses mammary tumor growth and reduces circulating exosome TGFB-beta content via beta-adrenergic receptor signaling in MMTV-PyMT mice. Breast Cancer (Auckl) (2020) 14:1178223420931511. doi: 10.1177/1178223420931511

170. Golden SA, Covington HE, Berton O3rd, Russo SJ. A standardized protocol for repeated social defeat stress in mice. Nat Protoc (2011) 6(8):1183–91. doi: 10.1038/nprot.2011.361

171. Hodes GE, Piuu MJ, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, et al. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. P Natl Acad Sci USA (2014) 111(45):16136–41. doi: 10.1073/pnas.1415191111

172. Coyne JC, Tenen H. Positive psychology in cancer care: Bad science, exaggerated claims, and unproven medicine. Ann Behav Med (2010) 39(1):16–26. doi: 10.1007/s12160-009-9154-z

173. Kraemer HC, Kuchler T, Spiegel D. Use and misuse of the consolidated standards of reporting trials (CONSORT) guidelines to assess research findings: Comment on coyne, stefanek, and palmer (2007). Psychol Bull (2009) 135(2):173–8. doi: 10.1037/a0015373

174. Mirsovic S, Jo B, Kraemer HC, Ershadi M, Neri E, Spiegel D. “Not just another meta-analysis”: Sources of heterogeneity in psychosocial treatment effect findings: Sources of heterogeneity in psychosocial treatment effect findings. Psychol Med (2009) 39(1):16–26. doi: 10.1017/S0033290908007137

175. Urech C, Grossert A, Alder J, Scherer S, Handschin B, Kasenda B, et al. Web-based stress management for newly diagnosed patients with cancer (STREAM): A randomized, wait-list controlled intervention study. J Clin Oncol (2018) 36(8):780–8. doi: 10.1200/JCO.2017.74.8491