CANCER

Psychological distress and eustress in cancer and cancer treatment: Advances and perspectives

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Facing cancer diagnosis, patients with cancer are prone to psychological stress and consequent psychological disorders. The association between psychological stress and cancer has long been a subject of high interest. To date, preclinical studies have gradually uncovered the promotive effects of psychological distress on tumor hallmarks. In contrast, eustress may exert suppressive effects on tumorigenesis and beneficial effects on tumor treatment, which brings a practicable means and psychosocial perspective to cancer treatment. However, the underlying mechanisms remain incompletely understood. Here, by focusing on the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, as well as stress-related crucial neurotransmitters and hormones, we highlight the effects of distress and eustress on tumorigenesis, the tumor microenvironment, and tumor treatment. We also discuss the findings of clinical studies on stress management in patients with cancer. Last, we summarize questions that remain to be addressed and provide suggestions for future research directions.

INTRODUCTION

The stress response consists of neuroendocrine cascades mediated by the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis through the release of stress neurotransmitters and hormones, including catecholamines (CAs) and glucocorticoids (GCs) (Fig. 1) (1). The stress response, also known as the “fight-or-flight” response, triggered by psychological, physical, or environmental stressors, can help someone fight against or flee from life-threatening problems (1). In 1974, Selye proposed two forms of stress: distress and eustress (2, 3). When stress is prolonged or exceeds the endurance of organisms, they may experience distress, which may induce a pathological condition. In contrast, moderate stress can help people cope with stressors and adapt to the environment.

On the basis of this theory, more and more researchers are aware of the double-sided effect of stress (4, 5). However, the term stress is still widely used in contexts where it actually refers to distress, i.e., bad stress. Here, we define the term distress broadly as a negative and unpleasant physical or psychological situation arising when the stress is too overwhelming or persistent. Psychologically, distress can be considered as a negative psychological state under pressure (6). Distress is not the same as mental illness. In the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases systems, there are no clinical diagnosis criteria for distress, while it mainly serves as an assessment dimension of dysfunction in other psychological disorders (7). In existing research, distress has been assessed by scales such as the profile of mood states short form (8) or general health questionnaire (9). The National Comprehensive Cancer Network considers patients with mental illnesses such as depression at high risk for moderate or severe distress (6). Therefore, distress should include diagnosed mental illnesses, as well as anxiety and depressive symptoms that do not meet the diagnostic criteria.

The term eustress is used less frequently than the term distress and is often misused due to inconsistent definitions in different fields (4). Generally, eustress can be characterized by short duration, optimal amount, and good experience (10). Therefore, we define eustress as the opposite of distress, that is, a positive condition with short-term, moderate, and agreeable stress. Eustress can reduce depression/anxiety-like behavior in stressed mouse models (11, 12), indicating that it may be a protective factor for mental illness.

Therefore, the relationship between stress and its effects can be described as an inverted U shape (Fig. 2). Stress below the threshold to trigger a stress response may fail to mobilize the body, while severe or chronic stress may lead to distress and later pathological conditions. Only moderate and short-term stress can serve as eustress and improve adaptability to stressors (2, 3).

Cancer diagnosis can become a high and chronic stressor, and thus contribute to persistent psychological distress in patients with cancer (5). On the one hand, cancer patients with psychological distress are more likely to be diagnosed with psychological disorders (13, 14). On the other hand, psychological distress is associated with increased cancer incidence (15, 16) and worse prognosis (9, 17). Preclinical studies have demonstrated that distress can promote tumorigenesis, tumor progression, and metastasis, as well as impair antitumor therapy (5). In contrast, recent animal experiments illustrated that environmental eustress can not only improve chronic stress–induced depression–like behavior (18) but also inhibit tumor growth and attenuate treatment resistance (19, 20).

Here, we summarize the effects and potential mechanisms of both psychological distress and eustress on tumorigenesis, the tumor microenvironment (TME), and tumor therapy. In addition, we review clinical studies of interventions targeting psychological stress in patients with cancer. We also discuss existing limitations and provide suggestions for future research directions.

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Psychological, physical, or environmental stressors can induce the stress response. There are two main neuroendocrine response systems involved, the SNS and HPA axes. The box lined blue shows the components of the SNS. The locus coeruleus can secrete norepinephrine (NE) and activate the SNS in response to stress. Upon activation, the terminals of sympathetic postganglionic nerves secrete vesicles containing NE. Sympathetic nerves also innervate the adrenal medulla, inducing it to synthesize and secrete NE and epinephrine. The box lined pink shows the components of the HPA axis. Corticotropin-releasing hormone (CRH) secreted by the hypothalamus acts on the pituitary gland to stimulate secretion of adrenocorticotropic hormone (ACTH), which promotes the secretion and release of GCs from the adrenal cortex.

**PSYCHOLOGICAL DISTRESS AND CANCER**

**Epidemiology**

There is evidence that psychological distress may increase the risk of cancer (15, 16). Cancer patients with psychological distress are more prone to psychological disorders (13, 14). Psychological stress may also affect cancer prognosis. Both psychological disorders and distress are related to higher mortality in patients with cancer (9, 17).

**Preclinical models**

Psychological distress in preclinical models can be induced by physical or social stressors (Table 1). Physical restraint (21–26) is a commonly used physical stressor, and there is also a method based on restraint, exposing mice to predator scent (27, 28). Social stressors include social isolation (21), repeated social defeat (22), and social disruption (29). Witnessing a conspecific mouse receiving an electric shock combines both physical and social stressor to induce stress in mice (30).

Moreover, some studies applied unpredictable stressors including physical restraints, light changes, isolation, and crowding randomly and repeatedly to induce distress in mice (31).

Stress does not necessarily translate into psychological distress. Therefore, it is necessary to confirm the distress paradigms by depression/anxiety-like behavior tests (Table 2). In animal models, depression/anxiety-like behavior can be characterized by decreased exploratory behavior (22) and despair behavior (22), with the locomotion tracks recorded by the camera for later software evaluation. The sucrose preference test (30, 32) is the most commonly used method to detect anhedonia. Despair behavior can be assessed by forced swimming (32) and tail suspension test (32). Social avoidance (22) is mostly used for evaluating social stressor–induced psychological distress.

Model animals are subjected to stressors of different duration and frequencies to mimic acute or chronic stress. There are no specific definitions and time criteria for acute and chronic stress (5). In preclinical studies, duration or frequencies of stimulation for chronic or acute stress paradigms vary by the type of stressor. For example, 2-hour daily restraint for 21 days (23) or unpredictable stressors for 6 days (31) can be used for inducing chronic stress in animal models. Previous studies illustrated that both acute and chronic stress could induce depression/anxiety-like behavior and promote tumor growth in mice (21, 22, 27). However, the difference in biological effects on tumors caused by acute and chronic stress is unclear. Apart from duration, the sequence of establishing distress models and transplanting tumor cells should be taken into consideration. In preclinical studies, mice have been exposed to stress before tumor inoculation (29, 33), after tumor formation (21, 23), or both (24, 25). Spontaneous tumor mice such as Hi-Myc mice (27) and LSL-Kras+;LSL-Trp53+/R172H;Pdx1-Cre (KPC) mice (28) were also used in studies to observe the effects of distress. These models can be used for exploring the impact of distress at different stages of tumorigenesis and disease progression.

In distress-tumor models, distress can be biologically defined as an excessive stress response that is strong enough to induce depression/anxiety-like behaviors and a series of biological processes.
in vivo such as DNA damage, angiogenesis, and immune suppression (5). The details will be described in the following sections.

**Effects on tumorigenesis, tumor progression, and metastasis**

**Tumorigenesis**

Although the clinical evidence of the association between psychological distress and tumorigenesis is still controversial (34), some preclinical studies have suggested the possibility of distress involved in tumorigenesis. DNA damage can cause somatic mutations and genomic instability, which may promote tumorigenesis (35). A potential mechanism by which psychological distress promotes the initiation of cancer is that distress may induce DNA damage through β-adrenergic receptor (β-AR) signaling. Stress-related norepinephrine (NE) can induce DNA damage in the presence or absence of carcinogens (36, 37) and prevent the repair of damaged DNA (38). β2-AR–mediated attenuation of p53 levels can increase the accumulation of DNA damage in response to chronic stress (39). Elevated GC levels can also suppress p53 function, which may induce chronic stress–induced tumorigenesis (40). In addition to inducing DNA damage, chronic stress facilitated lung tumorigenesis by enhanced exocytosis of insulin-like growth factor 2 in lung epithelial cells through phosphorylation of L-type voltage-dependent calcium channels induced by β-AR signaling (41).

**Tumor progression**

During tumorigenesis, tumor had acquired various characteristics and capabilities. Preclinical studies have indicated that distress may promote tumor progression by enhancing hallmarks of cancer, including inhibiting apoptosis, promoting angiogenesis, and regulating energy utilization (35).

Distress may help tumor cells evade apoptosis. Through β-AR signaling, distress up-regulates the expression of antiapoptotic myeloid cell leukemia 1, B cell lymphoma-2 (BCL-2), BCL-XL, and BCL-XL/BCL-2–associated death promoter (42), thus reducing tumor cell apoptosis. Moreover, chronic stress can enhance stem cell properties of breast cancer cells with up-regulated expression of self-renewal–related genes to promote tumor growth (24).

Animal studies showed that chronic stress promoted tumor angiogenesis in mice with ovarian carcinoma by up-regulating vascular endothelial growth factor (VEGF) expression in tumor tissue through β2-AR–activated cyclic adenosine 3’,5’-monophosphate (cAMP)–protein kinase A (PKA) signaling (43). This result was consistent with the conclusion from an in vitro study that treatment with NE, a main player

| Table 1. Psychological distress models in cancer. |
|-----------------------------------------------|
| **Stress procedure** | **Details** | **Duration** | **Reference** |
| Physical intervention | | | |
| Restraint | Mice were restrained individually in 50-ml ventilated centrifuge tubes. | Acute stress: 1 hour/day for 3 days | (21–26) |
| | | Chronic stress: 2 hours/day for 21 days | |
| Immobilization and exposure to predator scent | Mice were restrained individually in a ventilated conical vial, which was placed in a box with tissue penetrated by fox urine. | Acute stress: 1 hour | (27, 28) |
| | | Chronic stress: 1 hour/day for 7 days | |
| Social intervention | | | |
| Social isolation | Mice were housed individually. | During the whole experiment | (21) |
| Repeated social defeat | A mouse was introduced into a home cage of an aggressive heterospecific mouse (CD-1 mouse) for 10-min physical interaction. Then, a perforated glass divider was placed to physically separate two mice but allowed them sensory interaction for 24 hours (change the aggressor daily to avoid habituation). | Chronic stress: Exposure/day for 10 consecutive days | (22) |
| Social disruption | An aggressive mouse was placed periodically into a group of mice that have established social hierarchy (change the aggressor daily to avoid habituation). | Chronic stress: 2 hours/day for six consecutive days | (29) |
| Exposure to conspecific mice being electric shocked | Mice were placed in two-chambered shuttle boxes with a perforated transparent glass partition to witness a conspecific mouse receiving inescapable foot electric shock. | Exposure to 26-min foot shock/day on days 1 and 6 | (30) |
| Mixed intervention | | | |
| Unpredictable stress | Mice were exposed to different stressors daily, including cage tilt, isolation, crowding, damp bedding, rapid light-dark changes, and overnight illumination. | Chronic stress: Five consecutive days | (31) |
Table 2. Depression/anxiety-like behavior tests in mouse models.

| Behavior tests               | Details                                                                 | Parameter and its correlation with anxiety/depression | Reference |
|------------------------------|-------------------------------------------------------------------------|------------------------------------------------------|-----------|
| **Exploratory behavior**     |                                                                         |                                                      |           |
| Elevated plus-maze test      | Mice were placed in an elevated plus-maze, which is a cross-shaped apparatus elevated above the floor, consisting of two open arms, two closed arms and a central square area. Mice were allowed to explore freely in the maze for 5 min. The time each mouse spent in the open arms was recorded. | The time mice spent in the open arms: Negative correlation | (30)      |
| Open-field test              | Mice were placed in the corner of open boxes individually and allowed to explore freely for 0.5 or 1 hour under dim light conditions (5 or 10 lux). The locomotion of tracks of each mouse was recorded by camera and evaluated by software. | Total locomotion (length of the track): Negative correlation | (22, 30)  |
| Light-dark box test          | Mice were placed in the box with a dark chamber and a light chamber (~200 lux). Two compartments were connected with a door. The locomotion tracks of each mouse in the box and the time they stayed in the light chamber were recorded by a camera and evaluated by software. | Light chamber locomotion (length of the track): Negative correlation | (22)      |
| **Anhedonia**                |                                                                         |                                                      |           |
| Sucrose preference test      | Mice were housed individually in cages and supplied with equal-volume pure water and 1% sucrose solution for 24 hours (with food) or 3 hours (without food). The consumption of both liquids was recorded. | Sucrose preference [(sucrose consumption/(sucrose + water consumption) × 100%): Negative correlation | (30, 32)  |
| **Despair behavior**         |                                                                         |                                                      |           |
| Forced swimming test         | Mice were individually placed in a transparent vertical cylinder with water (about 25°C) for 6 min. The duration of immobility of each mouse after 1-min habituation was recorded. | Immobility duration: Positive correlation | (32)      |
| Tail suspension test         | Mice were hung upside down by their tails that were fixed at a certain height. The duration of immobility of each mouse after 1-min habituation was recorded. | Immobility duration: Positive correlation | (32)      |
| **Social behavior**          |                                                                         |                                                      |           |
| Social avoidance tests       | Mice were placed in open-field arenas individually with an empty wire cage under dim light condition (5 lux) for 150 s. Later, an aggressive CD-1 mouse was placed in the wire cage. Their interaction was evaluated by the duration the mice spent in the area projecting 8 cm around the wire cage with a CD-1 mouse. | Interaction ratio [(time spent in the area around the cage with CD-1 mouse/time spent in the area around the empty cage) × 100%]: Negative correlation | (22)      |
involved in the stress response, can promote the expression and secretion of angiogenesis-related cytokines, such as VEGF, interleukin-8 (IL-8), and IL-6 by melanoma cells through the pathway mentioned (43, 44).

According to the Warburg effect, tumor cells rely primarily on anaerobic glycolysis for energy supply (35). Distress may promote tumor energy utilization by elevating the level of lactate dehydrogenase A, which executes the final step of the Warburg effect (24).

As mentioned above, β2-AR signaling has been shown to promote tumor progression in multiple ways. The feed-forward loops between tumor and nerve can enhance this effect. In a mouse model of typically highly innervated pancreatic ductal adenocarcinoma, stress activated the β2-AR/PKA pathway and elevated the secretion of nerve growth factor and brain-derived neurotrophic factor (BDNF), which induced axonogenesis with subsequent increased NE accumulation in the TME, which promoted tumor growth (28).

**Tumor metastasis**

Psychological distress may regulate the TME to promote tumor invasion and metastasis. Matrix metalloproteinases (MMPs) are related to extracellular matrix degradation and tumor cell migration (35). Administration of CAs can promote MMP-2 and MMP-9 secretion in various tumor cell lines (45, 46). Increased MMP activity may be related to β2-AR–induced signal transducers and activators of transcription 3 (STAT3), an important convergence point for signaling pathways in tumors (46, 47). Moreover, activated β2-AR signaling can lead to epithelial mesenchymal transition (EMT) promoting metastasis of tongue squamous cell carcinoma through the β2-AR/IL-6/STAT3 pathway (48).

Furthermore, distress can promote tumor metastasis by establishing a premetastatic niche. Chronic stress increased lung colonza
tion and metastasis in a breast cancer model by increasing monocye output in the premetastatic phase and macrophage infiltration in the premetastatic lung (31). Stress can increase M2 macrophage infiltration and the expression of macrophage-derived prometastatic molecules such as prostaglandin-endoperoxide synthase 2 (PTGS2), MMP-9, and VEGF to mediate stress-enhanced metastasis (49). Moreover, stress increased myeloid-derived suppressor cell (MDSC) infiltration in tumor and lung metastases, which up-regulated transforming growth factor–β, VEGF, and IL-10 to promote EMT and tumor metastasis (50).

Tumor cells can migrate through lymphatic vessels, and the remodeling of lymphatics may be an important step in the lymphatic metastatic process (35). The synergy of cyclooxygenase 2 (COX-2) expressed by macrophages and AR-activated VEGFC-VEGFR3 signaling may be involved in stress-induced lymph vasculature remodeling in mice, which can promote tumor cell dissemination (51). In summary, distress promotes tumor genesis, progression, and metastasis (Fig. 3A).

**Effects influencing the function and infiltration of immune cells**

**T cells**

Distress can affect T cell numbers in secondary lymphoid organs (52) and the TME (21, 26). Social isolation stress shortened survival in a breast cancer mouse model, which was associated with a reduction in activated T cells and splenic CD8+ cells (21). Moreover, stress accelerated pancreatic cancer growth in young mice by down-regulating tumor-infiltrating CD4+ T cells (52). The decrease in T cell numbers may be due to distress suppressing the migration of T cells from lymph nodes to tumors and impairing T cell proliferation. β2-AR agonists reduced the motility of T cells in lymph nodes (53). This was due to local vasconstriction induced by β2-AR signaling causing hypoxia in lymph nodes, triggering rapid calcium signaling in leukocytes and inhibiting cell motility. β2-AR signaling can impair the proliferative capacity of antigen-specific T cells in mice with lymphoma (54). This is consistent with the reduced proliferation capacity of T cells from lymph nodes of stressed mice (55).

Distress can also promote T cell exhaustion, characterized by reduced cytokine secretion, decreased effector function, and elevated inhibitory receptor expression (56). β-AR signaling impairs the cytotoxic effects of T cells (53). In contrast, blocking β2-AR signaling in CD8+ tumor-infiltrating lymphocytes (TILs) isolated from stressed mice increases the secretion of interferon-γ (IFN-γ), granzyme B, and IL-12a (56). Glucocorticoid receptor (GR) activation can also notably suppress T cells. Elevated GCs can inhibit T cell responses through GR-induced transcription of immunosuppressive genes (57). By up-regulating immunosuppressive Tsc22d3 expression in dendritic cells (DCs), social defeat stress–induced GCs suppressed IFN-γ–positive T cell activation and inhibited type I IFN responses, which are necessary for antitumor immune surveillance (22). Distress can increase the expression of inhibitory receptors on T cells. In restraint-stressed mice, programmed cell death protein 1 (PD-1) and LAG-3 were up-regulated on intratumoral CD8+ TILs (26). Blocking β-AR signaling in stressed mice increased PD-1, LAG-3, and Tim-3 expressed on CD8+ TILs (56).

The mechanisms underlying the promotion of the T cell– exhausted phenotype are unclear, but suppressed T cell metabolic reprogramming (56) and activated kisspeptin/Gpr54 signaling (26) may be involved. Activated T cells require large amounts of energy supplied by glycolysis and oxidative phosphorylation, and the process increasing cellular metabolism is called metabolic reprogramming (58). In vitro experiments revealed that treatment with adrenergic agonists inhibited the metabolism in CD8+ T cells (58). Restrained psychological distress also impaired glycolysis and oxidative phosphorylation in naive CD4+ T cells isolated from mouse spleens (59). Blocking β-AR signaling with propranolol in stressed mice promoted glycolysis and mitochondrial oxidative phosphorylation in CD8+ TILs and reduced the proportion of exhausted cells expressing inhibitory receptors (56). Stress–induced purine metabolism disorder in peripheral CD4+ T lymphocytes may be responsible for stress–derived depression–like behavior (59). In addition to regulating metabolism, distress may also promote T cell exhaustion through other pathways. Restrained stress increased not only the level of plasma kisspeptin, a neuropeptide that could affect T cell function, but also the expression of its receptor Gpr54 on T cells in tumor, spleen, and hypothalamus (26). The knockdown of Gpr54 inhibited lung cancer growth by suppressing T cell dysfunction and exhaustion.

**NK cells**

Distress was found to be associated with lower cytotoxicity of natural killer (NK) cells in patients with ovarian cancer (8). CAs can reduce NK cytotoxicity through β2-AR signaling (60). However, in social disruption models, NK cells in the spleen or lung have been activated through β2-AR receptor signaling (61).

Besides CAs, GCs can suppress the cytotoxicity of NK cells and down-regulate the expression of perforin, granzyme, and IFN-γ by GR–altered gene transcription or epigenetic modifications (62). However, the inhibition of NK cells by cortisol relied on the mediation of CAs and/or prostaglandins, as the effect could be reversed by blocking NE or prostaglandins rather than GR (63).
Regulatory T cells
Regulatory T (T\textsubscript{reg}) cells are a subset of CD4\textsuperscript{+} T cells that suppress immune responses, thereby maintaining homeostasis and self-tolerance (64). Activation of \( \beta\)-AR signaling enhanced the immunosuppressive effect of T\textsubscript{reg} cells by promoting T\textsubscript{reg} cell–mediated conversion of CD4\textsuperscript{+} Foxp3\textsuperscript{−} T cells to Foxp3\textsuperscript{+}-induced T\textsubscript{reg} cells and up-regulating the expression of cytotoxic T lymphocyte (CTL)–associated protein 4, an immune checkpoint, on T\textsubscript{reg} cells through the \( \beta\)-AR/cAMP/PKA pathway (65). In a mouse model of squamous cell carcinoma, chronic stress--induced high corticosterone levels increased T\textsubscript{reg} cell infiltration in tumors through up-regulating C-C motif chemokine ligand 22 (CCL22), while they decreased the numbers of CTLs and helper T cells in tumors through down-regulating cutaneous T-cell-attracting chemokine (CTACK)/CCL27 (66).

Myeloid-derived suppressor cells
Chronic stress--induced \( \beta\)-AR activation has been found to lead to an increase in MDSCs (67) and their accumulation in the spleen and tumor, promoting tumor growth, metastasis, and vascularization (68). Stress-induced \( \beta\)-AR signaling inhibited MDSC apoptosis and promoted MDSC survival through regulating STAT3 and the Fas-FasL interaction, respectively. In addition, \( \beta\)-AR activation up-regulated immunosuppressive arginase-1 and programmed death ligand 1 (PD-L1) expression in MDSCs, thereby altering their ability to inhibit T cell proliferation (68).

Chronic stress can also promote the mobilization of MDSCs. Through activating \( \beta\)-AR signaling, chronic restraint stress up-regulated the expression of C-X-C motif chemokine receptor 2 (CXCR2) and phosphorylation of extracellular-regulated kinase in MDSCs in the bone marrow and chemokine C-X-C motif ligand 5 (CXCL5) in tumors (25). Through the \( \beta\)-AR/CXCL5-CXCR2/Erk pathway, chronic stress mobilized MDSCs from bone marrow to spleen and tumor and promoted hepatocellular carcinoma growth in mice.

Tumor-associated macrophages
Tumor escape is associated with the switch of macrophages from the proinflammatory M1 type toward the anti-inflammatory M2 type (69). M2 polarization can be induced by GCs (69). In vitro, isoprenaline can promote precursor cell M2-like polarization in the presence of the M2 polarization stimulator IL-4, which can be inhibited by \( \beta\)-AR blockade (70). Stress increased M2–tumor-associated macrophage (TAM) polarization through \( \beta\)-AR signaling and promoted breast

![Fig. 3. Effects of psychological distress on the TME and underlying mechanisms. (A)](image)

1. Tumorigenesis
   - Genome instability

2. Tumor progression
   - Angiogenesis
   - Apoptosis
   - Glycolysis
   - Neurogenesis
   - NGF

3. Tumor metastasis
   - EMT
   - ECM degradation
   - Lympathic vasculature
   - Lymphatic metastasis

A. Antitumorigenic immune cells
   - IFN-\gamma
   - CD8\textsuperscript{+} T cell
   - NK cell
   - Cytotoxicity

B. Protumorigenic immune cells
   - T\textsubscript{reg} cell
   - M1-TAM
   - M2-TAM
   - MDSC

GCs and CAs produced by the hyperactivated neuroendocrine system are involved in tumor regulation in the following aspects by binding to their receptors. 1. Distress may promote tumorigenesis through DNA damage. 2. Distress can facilitate tumor progression through reducing tumor cell apoptosis and promoting angiogenesis, glycolysis, and neurogenesis. 3. Distress can promote tumor metastasis through establishing a prometastatic microenvironment and premetastatic niches and remodeling the lymphatic vasculature. (B) Schematic diagram of the effects of distress on tumor immune microenvironment. Distress can induce a suppressive TME through reducing infiltration and function of effector immune cells, such as T cells, DCs, and NK cells, and promoting infiltration and function of suppressive cells, including T\textsubscript{reg} cells, M2-TAMs, and MDSCs. NGF, nerve growth factor; ECM, extracellular matrix; PGE\textsubscript{2}, prostaglandin E\textsubscript{2}; CCR2, C-C motif chemokine receptor; GzmB, granzyme B; PD-L1, programmed death-ligand 1.
cancer growth and metastasis (49). In summary, distress disturbs antitumor immunity (Fig. 3B) by inducing hyperactivated SNS and HPA axes.

**Effects on cancer treatment**

Psychological distress can also impair the efficacy of various types of cancer treatments.

**Surgery**

Surgery is a radical cancer treatment, but it is also a strong stressor. Surgical stress has been associated with tumor progression and metastasis in both animals (71) and human patients (72). Psychological distress during surgery may affect the prognosis of patients after surgery. An 11-year follow-up study showed that greater postsurgical depressive symptoms in patients were associated with shorter survival (73). Operation, anesthetics, analgesics, and psychological factors can induce dysregulation of the neuroendocrine-immune system, which affects the prognosis of tumor patients (74). Therefore, the perioperative period is a critical window for physiological and psychological intervention to improve the prognosis of patients with tumor.

**Chemotherapy**

Distress has been shown to impair the efficacy of cytotoxic agents by inhibiting chemotherapy-induced tumor cell apoptosis. β2-AR signaling impaired paclitaxel-induced apoptosis in ovarian cancer cells by up-regulating dual-specificity protein phosphatase 1 expression to inhibit c-Jun N-terminal kinase-mediated c-Jun phosphorylation (75). Stress-activated β2-AR signaling regulates the levels of Bcl-2 family proapoptotic molecules, which contribute to the resistance of apoptotic effects to chemotherapy (27, 42).

Distress can also weaken chemotherapy effects by inducing DNA damage, thus perhaps modulating the chemotherapy-induced DNA damage response. Cell line experiments have shown that stress-induced DNA double-strand breaks reduce DNA damage caused by cisplatin and diminish the therapeutic effect of cisplatin (37). Stress hormone–induced DNA damage and phosphorylation of ataxiatelangiectasia-mutated-and-Rad3-related kinase (ATR) and its major downstream effector checkpoint kinase 1 (CHK1) further up-regulated the G1 cell kinase inhibitor p21 to halt breast tumor cells in the G0–G1 phase. Stress thus impaired the effect of paclitaxel, which targets cells in the S phase of the cell cycle (76). Furthermore, animal studies showed that distress can impair the antitumor efficacy of immunogenic cell death inducers, such as oxaliplatin and mitoxantrone, through inducing intratumoral and systemic immunosuppressive effects (22).

**Immunotherapy**

As previously mentioned, distress can modulate tumor infiltration and function of various immune cells. Therefore, it is not unexpected that distress can affect the efficacy of immunotherapy. Preclinical studies have found that distress impairs the effects of immune checkpoint inhibitors, tumor vaccines, and immune-stimulating agents.

Distress may influence the efficacy of immune checkpoint inhibitors via AR- or GR-regulated T cell function or the expression of immune checkpoints and their ligands. Activated β2-AR signaling reduced the response to anti–PD-1 and anti–4-1BB monoclonal antibodies (mAbs) in mice with lymphoma by suppressing proliferation and function of CD8+ T cells (54). In a solid tumor model of stress-induced resistance to anti–PD-1 mAbs, β2-AR blockade up-regulated the ratio of effector CD8+ T cells to CD4+ Treg cells, decreased CD8+ TILs expressing PD-1, and thus reduced treatment resistance in the stressed mice (77). GR signaling has been shown to cause increased PD-L1 and decreased major histocompatibility complex I expression in pancreatic ductal adenocarcinoma models, thus promoting tumor immune escape and impairing the effects of anti–PD-1 treatment (78). GR blockade can induce an immunologically active TME to reverse the resistance to anti–PD-1 mAbs in mice caused by GC administration or social distress (22, 78). Distress attenuated the antitumor effects of CpG-C, a novel Toll-like receptor-9 immunostimulatory agent, in metastatic tumor models by impairing CpG-C–induced NK-cell activity, which could be reversed by simultaneous inhibition of COX-2, as well as GR and β-AR signaling (33).

Psychological distress can also affect the efficacy of tumor vaccines. The potential mechanism is inhibiting effector T cell function directly and/or indirectly preventing T cell activation. By preventing DCs from migrating into lymph nodes and activating CD8+ T cells, distress reduced IFN-γ-producing CD8+ T cells and CTL-mediated killing, which may account for the resistance to poly(o, l-lactide-co-glycolide) microsphere–based cancer vaccines in mice (29). Repeated social defeat stress negatively affected the response to prophylactic tumor cell vaccination by up-regulating the expression of GC-inducible factor Tsc22d3 in DCs, which can inhibit DC function and IFN-γ+ T cell activation, and such resistance can be reversed when a GR antagonist is present (22).

**Radiotherapy**

Distress may induce resistance to radiotherapy by suppressing radiation-induced antitumor immunity. Cool housing temperature stress impaired the response to irradiation in mouse models with a decrease in the percentage of CD4+ and CD8+ T cells expressing IFN-γ and granzyme B in tumors (79). Moreover, such stress can inhibit tumor responses outside the irradiated field, namely, the radiation-induced abscopal effect (80). Through β2-AR signaling, stress down-regulates T cell effector function and migration-related gene expression, hence decreasing IFN-γ, tumor necrosis factor–α (TNF-α), and granzyme B secretion and inhibiting CXCR3/CXCL9 signaling, while β2-AR signaling blockade can enhance T cell–mediated antitumor immune responses in both irradiated and distant unirradiated tumors (80).

EMT is associated with increased tumor invasion and contributes to tumor metastasis (35). Distress may also affect the efficacy of radiotherapy by regulating EMT-related pathways. Psychological stress–induced tumor progression and radiation resistance in mice with lung cancer may be the result of adrenergic-activated Wnt/β-catenin signaling with up-regulated expression of Wnt1, drosa, and vimentin and down-regulated E-cadherin in tumors (30).

**Targeted therapy**

Distress can affect the effects of antiangiogenic drugs and targeted inhibition of the epidermal growth factor receptor (EGFR) in mouse tumor models. For example, sunitinib exerts antitumor effects by inhibiting tumor angiogenesis. NE can attenuate the efficacy of sunitinib by up-regulating proangiogenic VEGF, IL-8, and IL-6 (81). Restrain stress impaired sunitinib antitumor effects through the same mechanisms in mouse colorectal tumor models, which can be reversed by propranolol (23).

EGFR–tyrosine kinase inhibitors (EGFR-TKIs) can suppress tumor cell proliferation through inhibiting EGFR autophosphorylation and blocking signal conduction. IL-6 serves as a main mediator in T790M-independent EGFR-TKI resistance (82). Stress hormones can...
Table 3. Effects and potential underlying mechanisms of distress on cancer treatment in preclinical studies. ↑, increase; ↓, decrease; →, causal; E, epinephrine; MCL-1, myeloid cell leukemia 1; BAD, Bcl-xl/Bcl-2–associated death promoter; ISO, isoprenaline; PLC, phospholipase C; PKC, protein kinase C; CREB, cAMP response element-binding protein; DUSP1, dual-specificity protein phosphatase-1; JNK, c-Jun N-terminal kinase; Chk1, checkpoint kinase 1; NSCLC, non–small cell lung cancer; APC, antigen-presenting cells; GzmB, granzyme B; LKB1, liver kinase B1.

| Treatments | Role of stress | Cancer type | Model | Stress | Specific effects or pathway | Reference |
|------------|----------------|-------------|-------|--------|-----------------------------|-----------|
| Chemotherapy | | | | | | |
| Cisplatin | Antiapoptosis | Pancreatic cancer | Mice | Cold stress (22°C versus 30°C) | β2-AR → ↑ anti-apoptotic molecules (MCL-1, BCL-2, and BCL-XL) | (42) |
| PI3K inhibitor, bicalutamide | Antiapoptosis | Prostate cancer | Mice | Immobilization stress; stress hormone (E) | β2-AR/PI3K/Akt/BAD antiapoptotic signaling pathway | (27) |
| Paclitaxel, cisplatin, or docetaxel | Antiapoptosis | Ovarian cancer | Cell lines; mice | Stress hormones (NE); β2-AR agonist (ISO); restraint stress | β2-AR/cAMP/PLC/PKC/CREB → ↑ DUSP1 → ↓ JNK-mediated phosphorylation of c-Jun | (75) |
| Cisplatin | DNA damage | Epithelial ovarian cancer | Cell lines | Stress hormone (NE) | β2-AR → ↑ DNA double strand breaks | (37) |
| Paclitaxel | DNA damage | Triple-negative breast cancer | Cell lines; mice | Stress hormones (cortisol, NE); restraint stress | Stress hormone → DNA damage → ATR/Chk1/p21 → tumor cell cycle halt in the G1 phase. (Paclitaxel targets cells in S phase) | (76) |
| Immunotherapy | | | | | | |
| Immunogenic cell death inducer; tumor vaccination, anti–PD-1 mAb | Immunosuppression | NSCLC; fibrosarcomas; colorectal cancer | Mice | Repeated social defeat stress; acute restraint stress | GC → ↑ Tsc22d3 → ↑ type I IFN responses in DC, activation of IFN-γ+ T cell | (22) |
| Tumor vaccination | Immunosuppression | Melanoma | Mice | Social disruption stress | Stress → ↓ DC function and migration to draining lymph nodes, APC priming → ↓ IFN-γ + CD8+ T cell, CTL-mediated target cell killing | (29) |
| CpG-C | Immunosuppression | Mammary carcinoma; colon tumor with liver metastasis; melanoma | Rats and mice | Wet cage stress | Stress → ↓ β2-AR, GR, COX-2 → ↓ cytotoxicity of NK cells by CpG-C | (33) |
| Anti–PD-1 mAb, anti–4-1BB mAb | Immunosuppression | B cell lymphoma | Mice | β-AR agonist (ISO) | β2-AR → ↓ proliferation, IFN-γ production, and cytolytic killing capacity of antigen-specific CD8+ T cells. | (54) |
| Anti–PD-1 mAb | Immunosuppression | Mammary carcinoma; melanoma | Mice | Cold stress (22°C versus 30°C) | β-AR → ↓ the ratio of effector CD8+ T cell and CD4+ regulatory T cell ratio (IFN-γ+ CD8+ T cell; Treg); ↓ PD-1 expression in effector CD8+ TILs | (77) |
| Radiotherapy | | | | | | |
| Local irradiation | Immunosuppression | Colon tumors; melanoma; mammary carcinoma | Mice | Cold stress (22°C versus 30°C) | β2-AR → ↓ CD8+ T cell migration (CXCR3/CXCL9) and function (T-bet, IFN-γ, TNF-α, and GzmB) | (80) |
| Irradiation | EMT | Lung cancer | Mice | Exposure to a conspecific mouse receiving inescapable foot shocks | β2-AR → ↑ Biomarker of EMT expressed in tumor: Wnt1, Drosha, and vimentin, E-cadherin | (30) |
| Irradiation | Immunosuppression | Colon adenocarcinoma | Mice | Cold stress (22°C versus 30°C) | β2-AR → ↑ the percentage of IFN-γ+ GzmB+ CD4+ and CD8+ in tumor | (79) |
| Targeted therapy | | | | | | |
| Sunitinib | Angiogenesis | Colorectal cancer; colon carcinoma | Mice | Chronic restraint stress; stress hormone (NE) | β2-AR/cAMP/PKA → ↑ VEGF, IL-8 | (23) |
| EGFR-TKIs | | NSCLC | Cell lines; mice | Stress hormone (NE) | β2-AR/PKC/LKB1/CREB → IL-6– mediated EGFR TKI resistance | (83) |
promote IL-6–mediated EGFR-TKI resistance in both lung cancer cell lines and mouse models by activating the β2-AR/protein kinase C/liver kinase B1/cAMP response element-binding protein axis, which can be reversed by β-AR inhibitors or IL-6–neutralizing antibodies (83). In summary, distress can impair antitumor efficacy of different therapies (Table 3).

**PSYCHOLOGICAL EUSTRESS AND CANCER**

**Epidemiology**

The concept of eustress is rarely mentioned in epidemiological studies and is mainly investigated in animal experiments. However, some positive lifestyles can be considered as eustress and may influence cancer incidence and mortality. For example, leisure-time exercise has been associated with a lower risk for 13 cancers (84). Social support may be related to a lower risk of breast and ovarian cancer and better prognosis of patients with cancer (11, 12).

**Preclinical models**

Most current studies use an enriched environment (EE) to model eustress, which is a well-studied modeling approach in psychiatry studies and has gradually been applied in tumor studies (19, 85, 86). EE consists of a variety of toys, such as climbing frames, wheels or shelters, and sufficient social communication (87).

EE can regulate the expression of receptors such as the β-AR (19) and the GR (18, 88) and of neurotransmitters such as serotonin and dopamine (89, 90). Living in EE can reduce stress responses and depression in mice (91, 92).

**Effects on tumorigenesis and tumor progression**

**Tumorigenesis**

Preclinical studies have found that environmental eustress can inhibit tumorigenesis after tumor cell inoculation or carcinogen induction. EE delayed tumorigenesis after subcutaneous injection of B16 melanoma or MC38 colon cancer cells and even completely abrogated tumor growth in some mice, the potential mechanism of which was EE decreasing a mitogenic factor, leptin (85). Compared to the standard environment, EE decreased the genesis of hepatocellular carcinoma induced by carcinogens, which may be associated with up-regulated antitumor immunity (19).

However, the underlying mechanisms are not yet fully understood. The protumorigenic effect of chronic distress may be related to the accumulation of DNA damage (5). In contrast to distress, eustress exhibited a protective effect against DNA damage. For example, EE improved the response to DNA damage and the rate of DNA repair after radiation exposure (93).

**Tumor progression**

Preclinical models of tumor-bearing mice housed in EE illustrated that eustress can suppress tumor progression by regulating the secretome of adipocytes and oxidative metabolism in tumor cells. Some preclinical studies found that EE eustress activated the hypothalamic-sympathoneural-adipocyte axis and thus decreased leptin secreted by white adipocytes (85), whose role in promoting tumor development and metastasis had been demonstrated (94). In mice inoculated subcutaneously with melanoma or colon cancer cells, EE up-regulated hypothalamic BDNF expression, which reduced the expression and production of leptin in white adipocytes (85). β-AR signaling served as a peripheral pathway synergistically involved in these antitumor effects of EE by reducing leptin (85). In addition, by up-regulating brain BDNF, EE also reduced microglia/macrophage activation in an intracranial glioma model (86).

In addition to decreasing leptin secretion, eustress can also inhibit tumor growth through inducing interorgan signaling cross-talk and adipokine/cytokine secretion (95). Spontaneous physical activity of obese mice housed in EE limited mammary tumor growth. Multiple factorial analysis showed cross-talk of signaling pathways and of adipokine/cytokine secretion of tumor, adipose tissue, and muscles, decreasing the antioxidative response and inflammation in tumor tissue. Similarly, another study of mouse mammary tumor models showed that EE-suppressed tumor growth was associated with increased adiponectin/leptin ratio in blood plasma and decreased COX-2, an inflammatory factor and a crucial enzyme in the metabolic pathway leading to prostaglandin formation in tumors (96).

EE may also regulate intracellular oxidative metabolism in tumor tissues. Being housed in EE significantly reduced subcutaneous and orthotopic pancreatic tumor growth in mice. Integrative transcriptomic and proteomic analysis of dissected tumor tissue revealed that EE mainly down-regulated genes localized to mitochondria and related to oxidative phosphorylation and the citric acid cycle, which is a key metabolic pathway linking carbohydrate, adipose tissue, and protein metabolism (97). In addition to the above mechanisms, eustress can also inhibit tumor growth by promoting antitumor immunity, which will be described below.

**Effects influencing the function and infiltration of immune cells**

**T cells**

In contrast to distress, eustress can promote antitumor immunity through activating the SNS and HPA axes. This is consistent with the view that the moderate stress response in eustress can have protective effects.

In a melanoma model, CD8⁺ T cells were required to mediate the anticancer effects of an EE. EE increased the proportion of CD8⁺ CTL in secondary lymphoid tissue with no significant alteration in CD8⁺ T cells in the TME (98). The modulation of T cell immunity by EE was reversed by BDNF knockdown, β-AR, or GR blockade, indicating the involvement of the SNS and HPA axis.

In a hepatocellular carcinoma model, EE eustress also induced CD8⁺ T cell–dependent tumor suppression. Through the β-AR/CCL2 axis, EE increased CD8⁺ T cell infiltration and decreased M-MDSCs, G-MDSCs, and M2 tumor–associated macrophages in the TME (19).

**NK cells**

In general, eustress seems to promote cytotoxicity and infiltration of NK cells in tumor models. EE promoted maturation and proliferation of NK cells in blood, bone marrow, and spleen in a pancreatic cancer mouse model (99). A potential mechanism is that EE can up-regulate receptors or cytokines related to NK cell activation and proliferation.

NKG2D, an activating receptor expressed on NK cells and some T cell subsets, plays an important role in tumor immunosurveillance (100). EE-housed mice showed enhanced antitumor effects and tumor infiltration of NK cells with up-regulated expression of NKG2D and C-C chemokine receptor 5 on NK cells, which could be reversed by blocking β-AR signaling or chemical sympathectomy (20).

IL-15 can induce differentiation and proliferation of NK cells (100). By up-regulating brain IL-15, EE enhanced antitumor activity and levels of NK cells both in TME and peripheral blood of mice with intracranial glioma (86).
**Effects on cancer treatment**

Although there are few studies in this field, the existing studies show that eustress can significantly promote the efficacy of antitumor treatments. EE eustress can synergize with chemotherapy and immunotherapy. EE enhanced the response to 5-fluorouracil or gemcitabine in pancreatic tumor models (101). Microarray analysis showed that EE down-regulated expression of the tumoral adenosine triphosphate–binding cassette transporter A8b gene. Living in EE promoted CD8⁺ T cell–mediated antitumor immunity through β-AR/CCL2 axis and enhanced the response to PD-1 mAb in a PD-1–insensitive hepatocellular carcinoma model (19).

Exercise can be a factor of eustress and can improve the efficacy of chemo- and radiotherapy. Physical exercise can enhance tumor blood flow and reduce tumor hypoxia, which may decrease tumor aggressiveness and facilitate antitumor drug delivery (102). Exercise promoted chemotherapy efficacy and suppressed tumor growth in mice, which was associated with improved tumor perfusion (102). Moreover, physical exercise may up-regulate NK cell infiltration to enhance the antitumor efficacy of radiotherapy (103). Overall, studies showed that eustress may inhibit tumorigenesis and tumor progression and enhance antitumor treatments (Table 4).

**INTERVENTIONS TARGETING PSYCHOLOGICAL DISTRESS IN PATIENTS WITH CANCER**

**Psychological intervention**

Because of the prevalence of mental illness among patients with cancer and the potential promotion of cancer progression by distress, distress management is necessary and important. Psychological management significantly mitigates psychological distress and improves quality of life (QoL) of patients with cancer (Table 5) (104–110). However, the effects on long-term survival are still controversial. Psychological intervention can improve survival and reduce mortality and recurrence in patients with breast cancer (111, 112). However, in other studies, psychological interventions only reduced psychological distress but did not significantly improve survival of patients with cancer (113–118).

A flattened diurnal curve of cortisol rhythm is associated with psychological distress and even poor prognosis in patients with cancer (119, 120). Psychological intervention can maintain the diurnal cortisol profile with a steep slope (108, 121). Psychological intervention can also down-regulate the levels of stress-related inflammatory cytokines, such as IL-6 and TNF-α, and up-regulate antitumor immunomodulatory factors, such as IFN-γ (122, 123).

**Pharmacological blockade of the stress response**

On the basis of the stress response theory, targeting stress response mediators may prevent cascades induced by distress and improve antitumor effects in patients with cancer. There are not many studies in this field, and most of them have explored the role of β-AR blockade. β-AR blockers reduced expression of inflammatory genes induced by acute social psychological stress in healthy volunteers (124). A phase 1 clinical trial showed the safety, tolerability, and promising activity of the combination of propranolol and pembrolizumab in patients with melanoma (125). In some stress-prone phases, blocking the β-AR seems to be particularly useful. The peri-transplant period is a stress-prone phase in patients undergoing hematopoietic cell transplantation. Blocking the β-AR in this context is safe and feasible and can reduce stress-induced risk markers (126, 127).

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### Table 4. Effects and potential mechanisms of eustress on cancer treatment in EE models

| Cancer type                          | Effects on tumor | Effects on TME | Mechanism                                              | Reference |
|--------------------------------------|------------------|----------------|--------------------------------------------------------|-----------|
| Melanoma, colon cancer               | ↓ Tumorigenesis, growth | ↓ VEGF ↑ NK cell, CD8+ function | ↑ Hypothalamic-derived BDFN → ↑ β-AR → ↑ leptin ↑ lipocalin production in adipose tissue | (85)      |
| Intracranial glioma                  | ↓ Tumor growth   | ↑ IL-15, BDFN ↓ NK cell, microglia/macrophage | Cross-talk between changed signaling pathways and adipokine/cytokine secretions in muscle, adipose tissue, and tumor | (95)      |
| Mammary cancer                       | ↓ Tumor growth   | COX-2 expression | ↑ Intratumoral COX-2 → inflammatory state ↑ plasma ratio of adiponectin and leptin | (96)      |
| Mammary cancer                       | ↓ Tumor growth   | NR             | ↑ Mitochondria-related genes (encoding key enzymes of the citrate cycle and pyruvate decarboxylation) in cancer cells | (97)      |
| Pancreatic cancer                    | ↓ Tumor growth   | ↑ NK cell      | ↑ β-AR → ↑ expression of CCR5 and NKG2D on NK cell → ↑ NK cell function | (20)      |
| Pancreatic cancer, lung cancer       | ↓ Tumor growth   | ↑ Immune suppression | ↑ Immune suppression (↑CD8+ T; ↑ MDSC, M2-TAM) | (19)      |
| Hepatocellular carcinoma             | ↓ Tumorigenesis, growth | ↑ Response to anti-PD-1 mAb | ↑ SNS → β-AR → ↓ CCL2/CCR2 → ↑ chemotaxis of MDSC and M2-TAM | (19)      |
| Pancreatic cancer                    | ↑ Response to chemotherapy | NR             | ↑ Tumoral ATP-binding cassette transporter A8b | (101)     |
Table 5. Randomized controlled trials on psychological distress management in patients with cancer. NS, not significant; HR, hazard rate; MBSR, mindfulness-based stress reduction; MBCR, mindfulness-based cancer recovery; SET, supportive expressive group therapy; MCGP, meaning-centered group psychotherapy; CALM, cancer and living meaningfully; SGP, supportive group psychotherapy; PCS, physical component scale.

| Study                    | Patients (type; feature) | Intervention(n); time | Laboratory examinations | Psychological outcome | Survival effect | Other benefits                                      | Reference |
|--------------------------|--------------------------|-----------------------|-------------------------|-----------------------|-----------------|-----------------------------------------------------|-----------|
|                           |                          | Cognitive-existential group therapy (n = 154); 20 weeks control (n = 149); 20 weeks | NR                      | ↓ Anxiety             | NS (HR for death, 1.35; 95% CI, 0.76–2.39; P = 0.31) | ↑Family functioning (117) |
| Kissane et al. (2004)    | Breast cancer; early stage |                      |                         |                       |                 |                                                     |           |
| Andersen et al. (2008)   | Breast cancer; postsurgery | Psychological intervention (n = 114); 1 year control (n = 113); 1 year | NR                      |                       | ↓ Risk of breast cancer recurrence (HR, 0.55; P = 0.034); risk of death from breast cancer (HR, 0.44; P = 0.016) | NR (111) |
| Hoffman et al. (2012)    | Breast cancer; postsurgery | MBSR (n = 114); 8 weeks control group (n = 115); 8 weeks | NR                      | ↓ Total mood disturbance, anxiety | NR              | ↑ Breast cancer-related QoL and endocrine symptoms, well-being* (104) |
| Carlson et al. (2013)    | Breast cancer; with clinically meaningful distress | MBCR (n = 113); 8 weeks | SET (n = 104); 12 weeks | MBCR, SET: Steep diurnal cortisol slope | MBCR: ↓Stress level | NR MBCR: ↑QoL, social support (108) |
| Witek Janusek et al. (2019) | Breast cancer; newly diagnosed | MBSR (n = 84); 8 weeks control (n = 80); 8 weeks | ↑TNF-α, IL-6; ↓IFN-γ | ↓ Perceived stress, depressive symptoms | NR              | ↓Fatigue, sleep disturbance (122) |
| Breitbart et al. (2015)  | Various cancers; advanced | MCGP (n = 132); 8 weeks | SGP (n = 121); 8 weeks | NR                     | NS: Anxiety | ↑ Physical symptom distress (105) |
| Rodin et al. (2018)      | Various cancers; advanced | CALM (n = 151); 3 to 6 months usual care (n = 154); 3 to 6 months | NR                      | ↓ Depressive symptoms | NR              | NR (109) |

| Study                    | Patients (type; feature) | Intervention(n); time | Laboratory examinations | Psychological outcome | Survival effect | Other benefits                                      | Reference |
|--------------------------|--------------------------|-----------------------|-------------------------|-----------------------|-----------------|-----------------------------------------------------|-----------|
| Spiegel et al. (1989)    | Breast cancer; metastatic | SGP (n = 50); 1 year | Control (n = 36); 1 year | NR                    |                 | ↑Mean survival: 36.6 months versus 18.8 months (P = 0.00001, Cox; P = 0.005; log-rank) | NR (112) |
| Goodwin et al. (2001)    | Breast cancer; metastatic | SET (n = 158); ≥1 year | Control (n = 77); ≥1 year | NR                    | ↓Psychological symptoms | NS (univariate analysis: HR, 1.06; 95% CI, 0.78–1.45; P = 0.72; multivariate analysis: HR, 1.23; 95% CI 0.88–1.72; P = 0.22) | ↓Pain (113) |

continued on next page
SUMMARY AND FUTURE CONSIDERATIONS

Clinical and preclinical findings suggest virtually opposite effects of psychological distress and eustress on malignant tumors (Fig. 4). These effects are largely mediated by changes in the neuroendocrine-immune system, with the SNS and HPA axes appearing to be the most important mediators. However, there are still limitations in current studies on the effects of psychological distress and eustress on malignant tumors.

In preclinical studies of distress, there is still a lack of models that can mimic the distress experienced by patients, which is complex and unpredictable. Moreover, the timing of stimulation is seldom taken into consideration. For eustress, EE is a widely accepted modeling method. However, specific settings of EE vary in different studies. One question, therefore, is whether a standard and simplified EE model with comparable effects can be developed to improve the reproducibility.

Clinical findings on the effects of psychological stress on tumor control are still controversial. There are reciprocal, interactive, and bidirectional effects between psychological factors and tumors in patients with cancer. Therefore, the establishment of long-term and prospective clinical cohorts is important to uncover the influence of psychological distress and eustress on the risk and prognosis of cancer. Moreover, since the psychological stress faced by patients with tumor is complex, real-world studies are recommended to explore the association between psychological stress and patients’ outcomes.

To elucidate the mechanisms underlying the effects of psychological stress on malignant disease, multiomics studies, such as cytokomics, genomics, metabolomics, proteomics, and bioinformatics analytical approaches, can be applied to explore the key mediators of psychological distress and eustress in malignant diseases and to develop relevant targeted therapies or to find prognostic biomarkers. In addition to the SNS and HPA axes, other molecules associated with stress coping may also have effects on malignant tumors, including dopamine, serotonin, and oxytocin (89, 90, 128). And the
impact of these mediators on malignancies could be of interest in future studies.

Recently, polymorphic microbiomes have been added to the “hallmarks of cancer,” emphasizing the potential to regulate the antitumor immune response and other hallmarks of cancer (129). The microbiome of the host, e.g., the gut microbiome, can interact with the nervous system through the microbiota-gut-brain axis, which can be influenced by psychological factors (130). Apart from the gut, microbes also reside in other organs, such as the lung. A recently published study illustrated that lung microbiomes can affect brain microbes also reside in other organs, such as the lung. Apart from the gut, microbes also reside in other organs, such as the lung. Apart from the gut, microbes also reside in other organs, such as the lung. Apart from the gut, microbes also reside in other organs, such as the lung. Apart from the gut, microbes also reside in other organs, such as the lung.

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