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Invited Review

Cancer and stress: NextGen strategies

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Title
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Abstract

Chronic stress is well-known to cause physiological distress that leads to body balance perturbations by altering signaling pathways in the neuroendocrine and sympathetic nervous systems. This increases allostatic load, which is the cost of physiological fluctuations that are required to cope with psychological challenges as well as changes in the physical environment. Recent studies have enriched our knowledge about the role of chronic stress in disease development, especially carcinogenesis. Stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), resulting in an abnormal release of hormones. These activate signaling pathways that elevate expression of downstream oncogenes. This occurs by activation of specific receptors that promote numerous cancer biological processes, including proliferation, genomic instability, angiogenesis, metastasis, immune evasion and metabolic disorders. Moreover, accumulating evidence has revealed that β-adrenergic receptor (ADRB) antagonists and downstream target inhibitors exhibit remarkable anti-tumor effects. Psychosomatic behavioral interventions (PBI) and traditional Chinese medicine (TCM) also effectively relieve the impact of stress in cancer patients. In this review, we discuss recent advances in the underlying mechanisms that are responsible for stress in promoting malignancies. Collectively, these data provide approaches for NextGen pharmacological therapies, PBI and TCM to reduce the burden of tumorigenesis.
I Introduction

The fast pace of living in today’s society, income disparities and the current COVID-19 pandemic cause substantial anxiety and stress across the globe. This leads to a variety of well-known adaptive physiological changes, including blood pressure, heart rate, endocrine output and neuronal activity. All changes are needed to cope with psychological and physical challenges and to maintain balance within the body. But stress significantly disturbs the allostasis in human body. The essence of allostasis is that physiological systems are always fluctuating in order to adapt to environmental forces (McEwen, 2000). Depending on duration and intensity, physical and psychological stress can be acute or chronic (Krizanova et al., 2016). Acute stress relates to a sudden, short-term, single, non-repeating condition such as a traffic accident, an episode of violence, an unexpected disaster or the immediate effect of combat (Musazzi et al., 2017). In contrast, chronic stress is the result of long-term and often repeated exposure to psychogenic or physiologic stressors. This causes endocrine and behavioral responses that are regulated by a variety of the neurochemical systems (Russell and Lightman, 2019). This review focuses heavily on chronic stress because it is more relevant than acute stress to understanding and managing the health care of all types of cancer patients.

Chronic stress increases allostatic load because of the extra cost of these physiological fluctuations (McEwen and Stellar, 1993). There is already a known close relationship between stressful life events and numerous health disorders, especially clinical depression (Kessler, 1997; Maze, 1998). But solid evidence showing a link between stress and cancer has grown substantially in recent years. For example, an individual participant meta-analysis of 16 large prospective cohort studies reveal that higher levels of psychological distress are associated with greater mortality in both colorectal and prostate cancer patients (Batty et al., 2017). Similarly, data collected from a community sample of 15,453 individuals revealed that psychological stress is relevant to an increase in cancer mortality, especially in lung cancer (Hamer et al., 2009). Indeed, the very experience of being diagnosed with cancer and the anxiety and fear of living with the disease and its treatments lead to
poorer prognosis in breast cancer patients (Brown et al., 2020).

Following cancer diagnosis, surgery, chemotherapy and multiple cancer-related complications, the vast majority of cancer patients suffer from chronic psychological distress. This not only increases the allostatic load of patients but also promotes cancer progression (Sharpley et al., 2018). Stress affects a variety of tumor phenotypes, including proliferation, metastasis, genomic instability and angiogenesis. For example, recent preclinical evidence suggests that chronic stress activates tumor-promoting autophagy that enhances proliferation and metastasis in gastric cancer (Zhi et al., 2019). And growing studies have revealed that chronic stress causes various metabolic disorders and suppresses a variety of events in the immune system (Nemati et al., 2017; Stefanaki et al., 2018; Fali et al., 2018), both of which contribute to the failure of anti-tumor treatments (Reiche et al., 2004). Chronic stress enhances breast cancer stem-like traits by disrupting normal glucose metabolism (Cui et al., 2019). In mice, chronic restraint stress suppresses secretion of type I cytokines and protective T cells, thereby promoting tumorigenicity in squamous cell carcinoma (Saul et al., 2005). In addition, changes in the gut microbiota and disruption of circadian rhythms increase allostatic load, which is linked to physiological system disorders and cancer pathophysiological deterioration (McEwen, 2000; Wong et al., 2016). In the following sections, we will discuss in detail the effects of chronic stress on different phenotypes of tumors.

Chronic stress increases blood levels of epinephrine, norepinephrine and glucocorticoids by continuously activating the HPA axis and SNS (Sapolsky et al., 2000; Glaser and Kiecolt-Glaser, 2005). The increase in epinephrine, norepinephrine and glucocorticoids is closely aligned to the occurrence and development of various diseases (Popovic et al., 2017; Adzika et al., 2019). For example, elevated levels of circulating catecholamines cause metabolic disorders and calcium-handling abnormalities in patients with chronic diabetic cardiomyopathy, and these are closely aligned to the aggravation of cardiac dysfunction (Dhalla et al., 2019). Clinical studies have confirmed that elevated cortisol is positively associated with both cardiovascular disease incidence and a poor prognosis (An et al., 2016; Iob and Steptoe, 2019).
Recent studies have indicated that the increase in hormones caused by chronic stress is also quite relevant to the occurrence and development of tumors. Epinephrine and norepinephrine promote the malignant progression of tumors via increasing glucocorticoid secretion and activating $\beta$-adrenergic receptor (ADRB) signaling pathways, both of which are associated with increased incidence of tumorigenesis (Neeman et al., 2012; Ayroldi et al., 2018; Hiller et al., 2020). Similarly, the restraint-induced rise in plasma oxytocin increases metastasis to the lung in a melanoma model (Ji et al, 2019). In contrast, dopamine effectively reverses malignant proliferation of chronic, stress-promoted tumors (Moreno-Smith et al, 2011). A major objective of this review is to summarize the specific mechanisms by which chronic stress hormones regulate tumor development.

Potential therapeutic strategies for tumor progression caused by chronic stress are available. Since chronic stress hormones promote tumor progression by acting on ADRB signaling pathways, $\beta$-adrenergic blockers play an important role in improving prognosis (Shaashua et al., 2017). Accumulating studies conducted both in vivo and in vitro have confirmed that inhibitors of chronic stress-specific targets also play significant roles in suppressing carcinogenesis by reversing activation of chronic stress-related pathways (Hara et al., 2011; Yang et al., 2019). For example, the release of lactate dehydrogenase A (LDHA) caused by chronic stress promotes breast cancer stem-like properties, all of which are reversed by the LDHA inhibitor vitamin C (Cui et al., 2019). Of note, numerous PBI also improve the effectiveness of anti-tumor therapies by reducing the psychological burden of cancer patients. These include psychotherapy (Temel et al., 2010), yoga therapy (Lin et al., 2019), music therapy (Bradt et al., 2016) and mindfulness training (Pathrose et al, 2020). Indeed, a thoughtful and insightful short commentary has highlighted the benefits of music for improving mental health, combatting the detrimental effects of stress and improving quality of life (Simon, 2015). Cancer patients usually also suffer from numerous physical side effects such as nausea, vomiting, dyspepsia and sleep disruption during radiotherapy and chemotherapy. These are treated with a combination of TCM approaches. For example, clinical data have shown that acupuncture and Tai Chi have
important roles in improving the prognosis and quality of life by alleviating cancer-related pain and fatigue (He et al., 2019; Kinney et al., 2019). As will be discussed in this review, many other potential therapeutic strategies are awaiting exploration.

**II Regulation of stress-induced hormones in cancer**

Chronic stress stimulates the HPA axis and SNS leading to increased glucocorticoids, plasma epinephrine and norepinephrine. Similarly, chronic stress increases plasma oxytocin but leads to a reduction in intratumoral levels of dopamine, the direct precursor of norepinephrine (Fig. 1). Recent evidence suggests that epinephrine, norepinephrine and glucocorticoids promote tumor initiation and progression that is closely aligned with high malignancy and poor prognosis (Pu et al., 2017; Lutgendorf et al., 2011; Yang et al., 2019). Stress activates cells in the hypothalamic paraventricular nucleus to release corticotropin-releasing factor (CRF). This CRF binds to its receptor in the adenohypophysis, leading to the secretion of adrenocorticotropic hormone (ACTH) (Westfall et al., 2019). ACTH stimulates release of glucocorticoids from the adrenal cortex, which increases tumor proliferation and metastasis. In addition, chronic stress-mediated stimulation of the SNS causes chromaffin cells in the adrenal medulla to release epinephrine and norepinephrine (Glaser and Kiecolt-Glaser, 2005; Lagraauw et al., 2015) that then promote tumor cell proliferation, metastasis and angiogenesis. In the tumor microenvironment, SNS signaling induced by chronic stress drives tumor cell proliferation and metastasis (Kim-Fuchs et al., 2014). Chronic stress also causes release of prolactin and oxytocin from the pituitary gland. Prolactin accelerates breast cancer progression during chronic stress in a mouse model (Tejwani et al., 1991). In melanoma, oxytocin also promotes lung metastasis in a chronic stress mouse model (Ji et al., 2019). Dopamine is a neurotransmitter released from the hypothalamus that regulates physiological actions mainly by acting on dopamine receptor 1 (DR1) and receptor 2 (DR2) subtypes. In ovarian cancer, dopamine enhances drug delivery via DR1 and inhibits angiogenesis via DR2 to inhibit tumor growth in chronic stress conditions (Moreno-Smith et al., 2011; Moreno-Smith et al., 2013). Dopamine is
transported via the median eminence to the adenohypophysis to suppress prolactin production from the anterior pituitary and then prolactin increases the secretion of dopamine, creating a negative feedback loop. Dopamine has long been known to be the precursor of norepinephrine biosynthesis. Dopamine opposes some of the effects of epinephrine and norepinephrine by reversing the proliferation of tumors during chronic stress. In the following subsections, we describe the specific mechanisms by which chronic stress-induced hormones and neurotransmitters affect a variety of cancer types.

1. Epinephrine, norepinephrine and cancer

Chronic stress-induced epinephrine enhances LDHA-dependent glycolysis to promote the deubiquitination of MYC, thereby leading to an increase in the stem-like properties of breast cancer cells (Cui et al., 2019). A prostate-specific myc transgenic murine model was used to show that chronic stress-induced epinephrine activates the ADRB2/PKA/DAB pathway to promote prostate tumor growth and inhibit apoptosis during treatment with bicalutamide (Hassan et al., 2013). Similarly, chronic stress induces adrenal gland hypertrophy to release epinephrine that activates ADRB2-HIF-1α-dependent angiogenesis in a pancreatic tumor mouse model (Shan et al., 2013). Clinical data show that survival of pancreatic patients with high blood levels of epinephrine is significantly shorter than in patients with low levels of epinephrine (Pu et al., 2017).

Chronic stress-induced norepinephrine activates the ADRB-PKA pathway to promote lung epithelial cell transformation and lung tumorigenesis (Jang et al., 2016). Consistently, chronic stress-induced norepinephrine enhances α1- and β2-adrenergic receptor-stimulated EGFR transactivation to promote invasion and prevent anoikis in hepatocellular cell carcinoma (Li et al., 2014). Norepinephrine released by the adrenal gland during chronic stress drives AMPK-dependent autophagy. This enhances gastric cancer cell proliferation in subcutaneous xenografts in a gastric orthotopic xenograft mouse model (Zhi et al., 2019). In the clinic, norepinephrine levels are highest in malignant and advanced ovarian cancer patients. The elevated norepinephrine level is positively correlated with both tumor grade and stage (Lutgendorf et al., 2011).
In addition, chronic restraint stress-induced catecholamines promote metastasis of colorectal tumor cells to the liver in BALB/c nude mice (Zhao et al., 2015). However, a recent study reported that chronic stress promotes breast cancer metastasis in epinephrine-blockage mice. The norepinephrine released from sympathetic nerve terminals is detectable in blood plasma and may act as a driver of stress-promoted metastasis (Walker et al., 2019). Thus, additional experiments are needed to more precisely define the mechanism of chronic stress-induced norepinephrine on stimulating tumor metastasis in diverse tumor types.

2. Glucocorticoids and cancer

Dexamethasone, a synthetic glucocorticoid hormone, promotes proliferation and invasion of the colon adenocarcinoma T84 cell line by stimulating cdk1 gene overexpression (Tian et al., 2019). In a chronic restraint mouse model, stress-induced glucocorticoids promote ionizing radiation-induced tumorigenesis by attenuating tumor suppressor P53 protein level and function (Feng et al., 2012). Clinical data have confirmed that stress-induced plasma cortisol in cancer patients accelerates expression of tsc22d3 in peripheral blood mononuclear cells, an effect that is positively correlated with poor prognosis (Yang et al., 2019).

Furthermore, chronic stress-induced abnormal plasma glucocorticoids also causes glucocorticoid functional resistance in myeloid cells (Niraula et al., 2018). Similarly, chronic stress-impaired nuclear translocation of glucocorticoid receptors is closely aligned to insufficient inhibition of glucocorticoids in the NF-κB pathway (Quan et al., 2003). In addition, chronic stress-induced glucocorticoid resistance in mice increases the number of inflammatory macrophages in the brain and enhances microglial activation via amplifying expression of the pro-inflammatory cytokines IL-1β and TNF-α (Wohleb et al., 2012). Chronic inflammation promotes progression, invasion and metastasis of cancer cells (Matzner et al., 2019; Zhang et al., 2020) and is positively associated with poor prognosis (Dolan et al., 2017; Dolan et al., 2018). Thus, the signaling network that connects chronic stress-induced glucocorticoid overproduction and glucocorticoid is an area that needs to be better defined.

3. Other hormones and cancer
Prolactin activates the PRL-SRC-FAK-MAPK pathway to promote breast cancer invasion (Barcus et al., 2013). Consistently, chronic stress increases prolactin release to facilitate dimethylbenz[a]-anthracene-induced breast cancer in a mouse model (Tejwani et al., 1991). Furthermore, in a prospective clinical analysis of 307 breast cancer patients, high levels of prolactin were significantly positively correlated with the risk of in situ breast cancer (Tikk et al., 2015). However, in a cohort of 580 specific triple negative breast cancer patients, prolactin receptor (PRLR) genes were highly expressed in epithelial-luminal differentiation cell types and PRLR subtypes were associated with prolonged disease free survival (Lopez-Ozuna et al., 2016). As such, prolactin might be a new classification system for triple negative breast cancer and serve as a potential target for clinical therapies.

Exogenous oxytocin treatment inhibits the neurotoxicity of 6-OHDA to promote neuroblastoma and glioblastoma cell progression (Bakos et al., 2012). In addition, chronic stress significantly increases levels of oxytocin in rats (Jezova et al., 1995). This chronic stress-induced oxytocin activates the ERK-VEF/MMP-2 pathway to promote lung metastasis in a melanoma mouse model (Ji et al., 2019). However, in ovarian cancer cells, oxytocin treatment induces apoptosis and autophagy in vitro by activating oxytocin receptors, thus reversing ovarian cancer proliferation (Mankarious et al., 2016). These opposing effects of oxytocin in different types of malignancies are likely due to differences between in vivo and in vitro approaches, but certainly requires further investigation.

Dopamine treatment activates the DR1-cAMP-PKA pathway to enhance vascular stability of tumors, thereby increasing the efficiency of cisplatin delivery to tumors. This results in improved efficacy of cisplatin and the inhibition of tumor growth in ovarian cancer (Moreno-Smith et al., 2013). In addition, dopamine replacement reduces cAMP through DR2 and inhibits VEGF-mediated Src activation. This leads to inhibition of tumor angiogenesis and promotion of cell apoptosis and reverses the effect of chronic stress in promoting the processes involved in malignant ovarian cancer (Moreno-Smith et al., 2011). Dopamine also reduces VPF/VEGF-induced VEGFR-2 phosphorylation via DR2 to inhibit angiogenic activity, thereby inhibiting
tumor angiogenesis in an ovarian cancer mouse model (Basu et al., 2001). Furthermore, the DR2 receptor agonist quinpirole inhibits VEGF-mediated angiogenesis and reduces tumor growth in a lung cancer mouse model. As such, this DR2 receptor agonist may be a potential drug to inhibit tumor angiogenesis during chronic stress.

All these collective reports establish that, chronic stress disturbs hormone and neurotransmitter systems that act in a variety of ways to promote tumor progression. In the future, these changes specific clinical biomarkers can be used to evaluate the degree of malignancy and to predict cancer risk and follow treatment. Importantly, the regulatory network of chronic stress-induced hormones in cancer deserves substantially more investigations.

III Mechanisms that link stress to cancer

Recent studies have revealed that chronic stress exhibits diverse roles in regulating cancer progression by promoting cell proliferation, genomic instability, metastasis, angiogenesis, immune suppression and metabolic disorders. Dysregulation of these biological processes promotes tumor development, leading to poor prognosis (Fig. 2).

1. Stress and proliferation

Uncontrolled proliferation is a crucial characteristic of most cancer cells. Chronic restraint stress-induced hormones promote cell proliferation and tumor burden in a variety of murine tumor models. In solid tumors, stress-induced norepinephrine activates a β2 adrenergic-neurotrophin feed-forward loop that promotes pancreatic ductal adenocarcinoma cell proliferation through sympathetic innervation and local norepinephrine accumulation (Renz et al., 2018). Chronic restraint stress-induced norepinephrine activates L-type voltage-dependent calcium channels (VDCC) through the ADRB-PKA pathway. This VDCC pathway triggers calcium mobilization that further enhances activation of the IGF receptor-signaling pathway to promote cell proliferation and lung tumorigenesis (Jang et al., 2016). Consistently, chronic restraint stress-induced norepinephrine triggers AMPK-dependent autophagy via ADRB2 to enhance cell proliferation in gastric
cancer (Zhi et al., 2019). In hematologic malignancies, chronic stress activates the SNS to activate the ADRB signaling pathway that accelerates progression of human pre-B acute lymphoblastic leukemia tumor load and cell proliferation. Importantly, the ADRB antagonist propranolol inhibits this effect (Lamkin et al., 2012). In contrast, daily restraint stress significantly reduces dopamine in tumors and surrounding tissues to promote cancer cell proliferation and tumor growth in both immunodeficient and immunocompetent mice in ovarian cancer models. This is reversed by dopamine supplementation (Moreno-Smith et al., 2011). Collectively, these data support the conclusion that chronic stress exhibits a critical role in cancer cell proliferation that enhances tumorigenesis (Fig. 2).

2. Stress and genomic instability

Genomic instability is a hallmark of cancer, including both the degree of chromosomal stableness and DNA damage. Previous studies have suggested that DNA damage is increased by exposure to stress and stress hormones (Gidron et al., 2006; Flint et al., 2007). Indeed, stress-related hormones cause DNA damage sufficient to promote transformation and tumorigenicity of mouse 3T3 cells, which is eliminated by treatment with the ADRB antagonist propranolol (Flint et al., 2013). Similarly, stress-induced cortisol shortens the length of telomeres that leads to activation of DNA damage responses in T lymphocytes (Choi et al., 2008; Song et al., 2010). In clinical studies, depression and anxiety of breast cancer patients may be an early step that leads to chromosomal instability (Lyon et al., 2014). In another study, (Aboalela et al., 2015), the effects of chronic stress on chromosomal instability were detected by a cytokinesis-blocked micronuclear/cytome assay in 71 breast cancer patients. The results show that breast cancer patients experiencing chronic stress are closely aligned with chromosomal instability frequencies as assessed by the Perceived Stress Scale during one year following chemotherapy. The underlying mechanism reveals that the chronic stress-induced release of β-adrenergic epinephrine and norepinephrine activates both the Gs-PKA and β-arrestin-mediated signaling pathways. These two changes trigger DNA damage and suppress p53 levels, respectively, thus synergistically leading to an increase in DNA damage (Hara et al.,
Unfortunately, not much more is known about the molecular pathways responsible for stress-induced DNA damage. As stress is a significant predictor of chromosomal instability (Fig. 2), there is a need for further mechanistic studies to explore the effects of stress hormones on DNA damage pathways involved in tumorigenesis.

3. Stress and metastasis

Chronic stress is involved in diverse critical steps of tumor metastasis, including metastatic niche formation, lymph node metastasis and distant metastasis (Fig. 2). First, chronic unpredictable stress promotes development of lung pre-metastatic niches by recruiting macrophages via the chemokine CCL2/CCR2 axis. This leads to lung metastatic colonization of circulating breast cancer cells in BALB/c mice (Chen et al., 2018). Furthermore, elevated epinephrine, norepinephrine and cortisol caused by restraint stress enhances gastric cancer invasion and lymph node metastasis by activating ADRB2. These effects are reversed by administration of an ADRB2-specific antagonist in both in vitro and in vivo models (Zhang et al., 2019). In addition, chronic restraint stress-induced catecholamines promote metastasis of colorectal tumor cells to the liver in BALB/c nude mice. The metastatic colorectal tumors exhibit heightened expression of metastasis-associated markers, including TGF-β, IL-6, PTGS2, MMP-9 and VEGF (Zhao et al., 2015). All of these biomarkers are reduced with β-blockers. Similarly, chronic restraint stress increases plasma oxytocin. This activates the ERK-VEGF/MMP-2 pathway via β-arrestin 2 to promote metastasis of melanoma cells to the lungs. Genetic knockdown of oxytocin receptors or β-arrestin 2 suppresses this chronic stress-induced increase in lung metastasis (Ji et al., 2019). In humans, β-blocker treatment prevented both lymph node metastasis and distance metastasis in a cohort of 956 breast cancer patients (Le et al., 2016). Thus, chronic stress promotes cancer metastasis to enhance both cancer complexity and diversity.

4. Stress and angiogenesis

Angiogenesis plays a crucial role in cancer progression. Previous studies have revealed that chronic stress promotes cancer angiogenesis by increasing cAMP-PKA
signaling, thereby elevating VEGF expression and inhibiting TSP1 (Fig. 2). For example, chronic restraint stress stimulates the cAMP-PKA signaling pathway via activation of ADRB2, and this increases vascularization that enhances ovarian tumor burden (Thaker et al., 2006). Similarly, chronic stress-induced norepinephrine suppresses anti-angiogenesis treatment through triggering of the ADRB-cAMP-PKA signaling axis (Liu et al., 2015). Furthermore, chronic restraint stress-induced epinephrine increases expression of VEGF to promote angiogenesis in pancreatic cancer via activation of the ADRB2-HIF-1α axis (Shan et al., 2013). Another type of chronic stressor, social isolation, also elevates VEGF/FGF2 via suppression of PPARγ, leading to breast cancer angiogenesis in vivo (Zhou et al., 2020). In addition, chronic restraint stress represses the function of HDAC2 to reduce expression of thrombospondin-1, an angiogenesis inhibiting factor, promoting angiogenesis in prostate cancer (Hulsurkar et al., 2017). In the clinic, the anti-angiogenic agents such as the USA Food and Drug Administration approved drug bevacizumab is widely used to inhibit tumor growth (Monk et al., 2016). Besides that, an inhibitor of VEGF receptors 1-3 (Lenvatinib) increases median survival times and decreases any-grade adverse events compared to the first-line treatment sorafenib in a phase III trial involving 954 non-resectable hepatocellular carcinoma patients (Kudo et al., 2018). Therefore, the combination of anti-angiogenesis and ADRB blockers might provide a potential therapeutic strategy to reduce tumor burden in chronically stressed cancer patients.

5. Stress and immune evasion

Accumulating evidence has led to the concept that immunosurveillance is critical for efficacious antitumor therapies (Yang et al., 2019). However, chronic stress tends to functionally suppress many aspects of the human immune system, which contributes to tumor immune escape (Hu et al., 2014; Matzner et al., 2020; Wieduwild et al., 2020). Several studies have demonstrated that chronic stress suppresses various protective immune responses, including those of T-cells, natural killer cells and macrophages (Antoni and Dhabhar, 2019). For example, elevated catecholamines induced by social disruption suppresses CD8+ T cell proliferation as well as
macrophage-derived IFN-γ in a breast cancer mouse model (Muthuswamy et al., 2017). Depression and anxiety suppress natural killer cell cytotoxicity and T-cell cytokine production in patients with ovarian cancer (Lutgendorf et al., 2008). Furthermore, chronic stress increases the number of immunosuppressive cells, including regulatory T-cells, regulatory B-cells and tumor-associated macrophages (Antoni and Dhabhar, 2019). For example, chronic stress enhances tumorigenesis in UV-induced squamous cell carcinoma by increasing regulatory/suppressor CD25+ T cells in a mouse model (Saul et al., 2005). Stress promotes CD11b+F4/80+ macrophage recruitment and M2 macrophage differentiation via activation of ADRB in an orthotopic breast cancer mouse model (Sloan et al., 2010). In addition, chronic stress plays an essential role in reducing the efficacy of many cancer immunotherapies. Specifically, social defeat elevates tsc22d3 expression that blocks IFN responses in dendritic cells and IFN-γ+ T cell activation. These effects are mediated by elevated glucocorticoids that leads to attenuated efficaciousness of anti-PD-1 tumor therapies (Yang et al., 2019). Stress caused by social disruption also suppresses CD8+ T cell responses via decreased dendritic cell maturation, leading to dendritic cell-based cancer vaccine therapy failure in melanoma (Sommershof et al., 2017). This immunosuppression caused by chronic stress serves as a potential cause for failure of at least some cancer therapies (Fig. 2). As such, these known links among chronic stress, immune system suppression and cancer therapy need to be further investigated.

6. Stress and metabolic disorders

Metabolic regulation is critical for maintaining numerous physiological functions in all organisms. Accumulating evidence has established that long-term exposure to chronic stress leads to a variety of metabolic disorders (Russell and Lightman, 2019). As but one example, chronic stress increases lysophosphatidylethanolamine and decreases sphingomyelin to dysregulate phospholipid and sphingolipid metabolism in the brain of rats (Oliveira et al., 2016). Chronic stress also decreases the hippocampal metabolites serine and threonine and aggravates cognitive impairment in APP/PS1 mice (Han et al., 2017). Furthermore, disruption of metabolic homeostasis contributes
to pathology in a number of diseases, including cancer. The glycolytic enzyme HK2 is required for tumor initiation and maintenance in mouse models of both kras-driven lung and erbb2-driven breast cancers. Ablation of hk2 is therapeutic in mice bearing lung tumors (Patra et al., 2013). Acyl-CoA-binding protein enhances glioblastoma tumorigenesis by accelerating fatty acid oxidation (Duman et al., 2019). In addition, recent studies have reported that chronic stress dysregulates metabolism to promote cancer progression (Fig. 2). For example, chronic stress promotes LDHA-dependent glucose metabolism rewiring to enhance MYC stabilization via USP28, contributing to breast cancer stem-like traits (Cui et al., 2019). In spontaneous breast cancer mouse models, social isolation promotes tumor burden and increases expression of a number of metabolic enzymes, including acc, acl and hk2 (Williams et al., 2009). As chronic stress triggers metabolic disorders through regulation of essential metabolic enzymes, targeting key enzymes could provide another effective therapeutic strategy for stress-related cancers.

7. Stress and other potential associated biological mechanisms

7.1 Circadian rhythms

The circadian clock serves as an important regulatory system that maintains circadian rhythms in normal cells and tissues (Sulli et al., 2019). Endogenous circadian rhythms are mainly established by two transcription-translation negative feedback loops, including the BMAL1-CLOCK and PERIOD-CRYPTOCHROME complexes (Kume et al., 1999; Takahashi, 2017). Disruptions in biological rhythms result in numerous physiological disorders with consequences that have been closely associated with several diseases, especially cancer (Sahar and Sassone-Corsi, 2009). For instance, loss of the core clock components per2 and bmal1 increases MYC expression, leading to cancer cell proliferation and metabolic dysregulation in a lung adenocarcinoma mouse model (Papagiannakopoulos et al., 2016). The CLOCK-BMAL1 complex elevates olfml3 to recruit immune-suppressive microglia into the tumor microenvironment, resulting in maintenance of glioblastoma stem cells (Chen et al., 2020).

The circadian clock is simultaneously synchronized with external environmental
cues such as light, ambient temperature and food intake to maintain proper
timekeeping in a variety of organisms (Masri and Sassone-Corsi, 2018). Chronic
psychological stress was reported to cause severe dysregulation of a variety of
rhythmic biological processes, including sleep-wake and neuroendocrine cycles
(Pillar et al., 2000; Hsiao et al., 2012). In a clinical study, subjective sleep disorders
exhibit a positive relationship with poor clinical outcomes and influence
chronotherapy effectiveness in metastatic colorectal cancer patients (Innominato et
al., 2015). Diurnal cortisol dysregulation in ovarian cancer patients is associated with
both fatigue and clinical depression (Weinrib et al., 2010). Thus, chronic
stress-induced circadian disruption is likely to serve as a negative prognosticator for
cancer prognosis.

7.2 Gut microbiota

Microbiota, often referred to as the “forgotten organ,” is defined as an ecological
community including about one hundred trillion microorganisms in the human
intestinal tract (Foster and McVey Neufeld, 2013). Recent studies have revealed that
gut microbiota exhibits critical roles in cancer progression by regulating the immune
system and bacterial metabolites. For example, the gut microbiome affects efficacy of
PD-1-based immunotherapy targeted to epithelial tumors. Oral supplementation with
*A. muciniphila* restores the efficiency of PD-1 blockade by increasing recruitment of
T lymphocytes into mouse tumor beds (Routy et al., 2018). Furthermore, altering
commensal gut bacteria induces liver-selective antitumor effects in both murine
primary and metastatic hepatoma models. This is regulated by gut
microbiome-mediated primary-to-secondary bile acid conversion that leads to an
increase in natural killer T cells (Ma et al., 2018).

A recent study reported that chronic restraint stress activates caspase-1 to affect
composition of the gut microbiome, leading to a reduction in the relative abundance
of *Akkermansia spp* and *Blautia spp*. and an increase in the *Firmicutes/Bacteroidetes*
ratio (Wong et al., 2016). Both *Escherichia coli* and *Bacteroides fragilis* promoted
tumor initiation in a mouse model (Dejea et al., 2018). The gut microbiome has also
been shown to communicate with the brain. For example, the gut microbiome is
associated with depression-like behavior and inflammatory processes in the ventral hippocampal cortex of stress-vulnerable rats (Pearson-Leary et al., 2020). But how chronic stress causes gut dysbiosis to promote cancer development remains unclear. These studies indicate that chronic stress-dysregulation of the gut microbiome may play a critical role in cancer progression. In addition, one recent study reveals that colonization with microbiota derived from autism spectrum disorder patients into germfree mice is sufficient to induce hallmark autistic behaviors (Sharon et al., 2019).

In further support of the potential importance of the gut microbiome in cancer, fecal microbial transplants from long-term survival patients or control donors can reduce the immunosuppressive properties of tumors and reduce tumor growth in a pancreatic adenocarcinoma mouse model (Riquelme et al., 2019). Thus, supplementation or elimination of tumor-specific gut microbiota may provide a potential therapeutic strategy for cancer patients experiencing chronic stress.

Taken together, these reports establish that chronic stress promotes tumorigenesis by increasing proliferation, genomic instability, metastasis, angiogenesis, immune evasion and metabolic disorders, while disrupting circadian rhythms and the gut microbiota community. In consequence, intervention in any of these specific molecular targets may provide new avenues for clinical cancer therapy. Importantly, regulatory networks that link chronic stress to any of these biological processes should be explored in future work.

IV Therapy for stress-induced tumor progression

Cancer patients usually suffer from varying degrees of chronic stress, and this is likely to further aggravate tumor malignant processes and weaken anti-tumor mechanisms (Antoni and Dhabhar, 2019). Appropriate therapies are efficient in improving anti-tumor therapy of cancer patients. These approaches for chronic stress-related cancer patients are β-adrenergic blockers, inhibitors of specific targets, PBI and TCM (Fig. 3).

1. β-adrenergic blockers

Chronic stress stimulates catecholamine release (Powell et al., 2013) that promotes tumor development through activation of the ADRB-signaling pathway.
Previous studies have shown that ADRB blockers have multi-anti-tumor effects in diverse types of cancers (Tang et al., 2013; Hollestein and de Vries, 2014; Coelho et al., 2017; Hiller et al., 2020). The nonselective ADRB blocker isoproterenol inhibits expression of MMP2 and MMP9 to reverse chronic stress-induced pancreatic cancer invasion. The ADRB2-specific antagonist ICI118,551 inhibits ERK1/2-JNK-MAPK signaling as well as oncogenic transcription factors to suppress chronic stress-triggered tumor proliferation and invasion in gastric cancer (Zhang et al., 2019). Similarly, in a hepatoma mouse model, administration of ICI118,551 significantly reduces tumor progression caused by stress hormones (Wu et al., 2016). In a tumor mouse model, propranolol reduces tumor burden caused by chronic stress and prolongs survival of mice (Partecke et al., 2016). A prospective nested case-control study including 4,113 pancreatic carcinoma patients and 16,072 matched controls showed that treatment with non-selective ADRB blockers for more than two years led to lower pancreatic cancer risk (Saad et al., 2020).

Since activation of ADRBs stimulates downstream specific targets to promote tumor progression, a combination of β-blockers and inhibitors of downstream specific targets represents a potential therapy for cancer patients. For example, treatment with the ADRB blocker propranolol and the COX-2 inhibitor etodolac significantly reduced host hepatic metastatic risk in a colon cancer mouse model (Sorski et al., 2016). In a clinical phase-II randomized trial, perioperative inhibition of COX-2 and ADRB signaling using propranolol and etodolac proved to be a safe and effective strategy for inhibiting metastasis and recurrence in breast cancer patients (Shaashua et al., 2017). Therefore, ADRB blockers are crucial in suppressing chronic stress-induced cancer progression.

However, the efficacy of β-adrenergic blockers in different types of cancer remains controversial. Both selective and nonselective β-adrenergic blockers cannot improve the overall recurrence rate and survival rate cancers with non-small cell lung cancer following resection (Cata et al., 2014). Different expression of β-receptors and the varying effects of catecholamines in specific tumor types may determine this outcome. In addition, non-selective β-adrenergic blockers have distinct affinities for
respective β-receptor ligands. For example, the β2/β1 selectivity ratio of propranolol is 8, while that of sotalol is 12 (Baker, 2005). Therefore, clinical trials are needed to determine the effect of β-adrenergic blockers on diverse tumor types and the therapeutic effects of various β-adrenergic blockers in cancer patients.

2. Inhibition of stress-specific targets

Accumulating evidence shows that chronic stress causes activation of a variety of signaling pathways to enhance oncogenesis, all of which are reversed by inhibition of specific targets. For example, chronic stress promotes p53 degradation to induce DNA damage, which is abrogated in arrb1-knockout mice (Hara et al., 2011). Furthermore, treatment with a glucocorticoid receptor antagonist or tsc22d3 deletion in dendritic cells rescues anti-cancer immune-surveillance systems to inhibit stress-induced tumor progression and improve therapeutic outcomes in mice (Yang et al., 2019). In addition, chronic stress-induced epinephrine promotes a breast cancer stem cell-like phenotype by activating LDHA-dependent metabolic rewiring, which is reversed by the LDHA-lowering agent vitamin C (Cui et al., 2019). As chronic stress elevates expression of cation chloride cotransporter Na\(^+\)-K\(^+\)-Cl\(^-\)-Cl\(^-\) (NKCC1) to cause the loss of GABAergic inhibition and the abnormal increase of stress-related hormones, the NKCC1 inhibitor bumetanide reverses chronic stress-related cancer symptoms (Gao et al., 2017). Overall, inhibition of chronic stress-regulated downstream targets might also serve as an effective strategy for cancer therapy. More molecular mechanisms and specific targets for promoting tumor progression under chronic stress are needed to be uncovered. Furthermore, the therapeutic effects of chronic stress-specific target inhibitors have been mostly evaluated only in cancer cells or animal models. These need to be supplemented with clinical trials on chronic stress-related targeted therapies.

3. Psychosomatic behavioral interventions

Cancer patients experiencing chronic stress are often burdened with a variety of adverse symptoms including (a) neuroendocrine dysregulation, (b) anxiety, depression and other mental health disorders, (c) sleep disturbances and (d) impaired quality of life. As highlighted below, all of these further accelerate cancer progression and lead
to poor overall survival. Intervention of these symptoms might provide a novel therapeutic strategy for cancer patients.

(a) Chronic stress often causes neuroendocrine disorders in cancer patients, such as abnormally increased production of cortisol, catecholamine and prolactin, as well as a reduction in dopamine levels. For example, breast cancer patients usually suffer from abnormal elevated plasma cortisol levels that contributes to breast cancer recurrence and poor prognosis (Hsiao et al., 2012). A cognitive-behavioral stress management (CBSM) intervention including relaxation, cognitive restructuring and coping skill training remarkably reduces psychological stress and plasma cortisol in breast cancer patients (Phillips et al., 2008). Furthermore, a study that included 242 adolescents has shown that the Mediterranean diet, characterized by a high monounsaturated-to-saturated fat ratio, high fruits and vegetables intake, coupled with a low intake of meat and dairy products, can reverse the abnormal increase in plasma cortisol caused by chronic stress (Carvalho et al., 2018). In a hepatoma tumor mouse model, moderate swimming on a regular basis (8 min/d, 9 weeks) increases dopamine levels, inhibits tumor growth and prolongs the rate of survival, while excessive swimming (16 and 32 min/d, 9 weeks) has the opposite effect (Zhang et al., 2016). In addition, massage therapy (30 min a session; 3 times/week, 5 weeks) significantly increases dopamine and serotonin levels and relieves stress symptoms in Stage I and II breast cancer patients (Hernandez-Reif et al., 2004). As chronic stress-stimulated prolactin release is associated with poor prognosis in cancer patients, oral administration of the dopamine receptor agonist cabergoline for 4 consecutive weeks (Lissoni et al., 2004) normalized blood prolactin and improved prognosis of breast cancer patients.

(b) Cancer patients with chronic stress often suffer from a series of mental disorders. Accumulated evidence has established that psychological distress, such as that caused by anxiety and depression, are associated with abnormal stress-related hormone levels that are closely relevant to cancer mortality (Strong et al., 2008; Walker et al., 2014; Choi et al., 2019). Previous studies have also shown that music therapy provided by trained music therapists is effective in reducing anxiety,
depression and other psychological disorders in cancer patients (Bradt, et al., 2016). In a randomized clinical trial involving 151 patients with metastatic non-small cell lung cancer, patients receiving early psychotherapy exhibited a significant improvement in a variety of psychological indices as assessed by the Anxiety and Depression Scale. This improvement in quality of life was associated with an increase in overall survival (Temel et al., 2010). Furthermore, non-purified diets made from natural ingredients effectively improved stress-induced depression- and anxiety-like behaviors in a mild social defeat stress mouse model (Goto et al., 2017). A single blind randomized controlled trial established that specific dietary intervention (protein 18% of total energy (E); fat 40% of E; carbohydrates 37% of E; alcohol 2% of E; fiber/other 3% of E) also improves mood and depressive symptoms in patients with moderate to severe diagnoses (Jacka et al., 2017). These results suggest that dietary interventions may provide an efficacious and accessible treatment strategy to reduce psychological distress in cancer patients. Moreover, physical activity (eg. chronic wheel running) increases galanin levels in the nucleus of mouse locus coeruleus, leading to a better stress resilience (Tillage et al., 2020). A randomized controlled trial, involving 116 lung cancer patients, has demonstrated that home-based moderate intensity walking exercise program (40 min/day, 3 times weekly, 12 weeks) is associated with reduced symptoms of both anxiety and depression (Chen et al., 2015). Compared with conventional cancer care programs, a personalized exercise program consisting of a combination of resistance, aerobic and flexibility exercises provided can effectively reduce symptoms of depression and fatigue (Marker et al., 2018).

Antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are widely used for cancer patients experiencing chronic stress. The SSRI fluoxetine effectively alleviates depressive symptoms of 163 advanced cancer patients based on a simple two-item questionnaire (Fisch et al., 2003). Similarly, the SNRI dezocine reduces depressive symptoms as evaluated by the Beck Depression Inventory of 120 colorectal cancer patients undergoing surgery (Zhao et al., 2020). As anxiety is another common symptom in cancer patients, the GABA analogue gabapentin has been shown to
relieve anxiety traits as measured by the Speilberger Strait-Trait Anxiety Inventory. Importantly, gabapentin exhibits a low risk of addiction or abuse compared with benzodiazepine, so it provides a safer therapeutic choice (Lavigne et al., 2012). It is noteworthy that another report with 128 patients with solid tumors shows that some of these findings could not be replicated. This study is organized as a randomized control trial and shows that psychotherapy is not particularly efficacious in ameliorating mental disorders, including anxiety, depression and despair (Breitbart et al., 2012). Collectively, these reports form the basis and strong justification for more informed studies on the role of comprehensive therapeutic strategies that include psychotherapy, dietary modification, specific exercises and medical interventions in well-defined populations of cancer patients.

(c) Chronic stress-induced sleep disorders are associated with tumor progression and a poorer prognosis. A study involving 67 participants establishes a significant correlation between self-reported chronic stress and self-reported poor sleep quality, as evaluated by the "Trier Inventory for the Assessment of Chronic Stress" (TICS) and the "Pittsburgh Sleep Quality Index" (PSQI) (Ohlmann et al., 2018). Another much larger study involving 11412 breast cancer patients showed that sleep disorders are positively correlated with cancer metastasis (Jacob et al., 2018). Thus, improvement of sleep quality in cancer patients may enhance the effectiveness of anti-tumor therapies. For example, a 3-month pilot randomized clinical trial confirms that diet rich in fruits, vegetables, whole grains and omega-3 fatty acids improves sleep quality and reduce fatigue in breast cancer patients (Zick et al., 2017). Furthermore, a nationwide multicenter phase III randomized controlled trial in the USA that recruited 410 cancer patients confirmed that yoga therapy is an effective means for improving sleep disorders and daytime dysfunction (Lin et al., 2019). Another randomized controlled trial involving 160 breast cancer patients finds that a 12-week machine-based progressive resistance exercise program ameliorates disturbed sleep during radiotherapy (Steindorf et al., 2017). In addition, a randomized, placebo-controlled trial that recruited 53 breast cancer patients shows that the phenylimidazole zolpidem improves sleep quality as assessed by the Pittsburgh Sleep
Quality Index and decreases wake time following sleep onset (Joffe et al., 2010). Melatonin, taken at bedtime for 2 months also improves sleep quality, subjective sleep, sleep fragmentation and sleep quantity as assessed in a clinical phase II trial with advanced breast cancer. As the latest research reveals that stress causes hyperarousal in mice through persistent activation of not only corticotropin-releasing hormone neurons but also hypocretin neurons (Li et al., 2020), inhibition of specific neuronal populations or related hormones provides a new target as a potential therapeutic strategy for stress-induced sleep disorder.

(d) Finally, chronic stress also impairs quality of life in cancer patients, and this can be ameliorated by a variety of complementary interventions. For example, a community extra life support program, including volunteer-provided palliative care services and hospice, significantly improves the quality of life in cancer patients (Walshe, et al., 2018). An 8-week web-based stress management program (STREAM) effectively improves quality of life in newly diagnosed cancer patients (Urech, et al., 2018). Furthermore, a follow-up study of 1,659 colorectal cancer patients shows that a higher consumption of ω-3 polyunsaturated fatty acids enhances physical function and reduces risk of cancer mortality (Song et al., 2017). Moreover, a high quality regular exercise program as assessed by the metabolic equivalent task score, improves overall quality of life in breast cancer patients (Chen et al., 2009). Supporting these results, a 12-week program, including weekly aerobic exercise and a nutritionally well-balanced 1200 kcal/day diet is shown to improve cardiopulmonary function and overall quality of life in breast cancer patients (Okumatsu et al., 2019).

Of note, cancer-related pain, fatigue and other adverse symptoms further aggravate chronic stress, leading to a decline in quality of life and a high risk of death in cancer patients (Deng et al., 2012; Hjermstad et al., 2016; Abrahams et al., 2018). For instance, several studies confirm that mindfulness-based intervention (purposeful, nonjudgmental, moment-to-moment awareness) relieves cancer-related pain, fatigue and mental distress (Rouleau et al., 2015; Al-Ghabeesh et al., 2019; Poletti et al., 2019). A dietary intervention with 56 colorectal cancer patients given Agaricus sylvaticus fungus (30mg/kg/day) for an average of 6 months results in a significant
decrease in cancer-related adverse symptoms and improved quality of life (Costa Fortes et al., 2010). A moderate- to high-intensity exercise program combined with resistant and aerobic training reduces pain, nausea, emesis and physical fatigue in breast cancer patients undergoing adjuvant chemotherapy (van Waart et al., 2015). According to a multicenter randomized controlled study which has recruited 240 cancer patients with moderate pain, both weak opioid and low-dose morphine alleviate cancer pain and improve life quality, as measured by the Edmonton Symptom Assessment System (Bandieri et al., 2016). Similarly, methylprednisolone therapy in 592 advanced cancer patients for 7 days effectively improves fatigue and appetite, as measured by the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (Paulsen et al., 2014). Another phase III randomized controlled trial among 243 cervical cancer patients shows that the eurokinin-1 (NK-1) receptor antagonist-fosaprepitant effectively decreases nausea and emesis symptoms, thereby improving life quality in cancer patients (Ruhlmann et al., 2016). Collectively, all these behavioral and psychological interventions provide a series of novel strategies to deal with chronic stress-induced adverse symptoms.

While these interventions including diet, stretching, aerobic and anaerobic exercises as well as traditional medicines may have little therapeutic effect when used singly (Su, 2019), they are generally innocuous in terms of producing serious side effects. And there are important caveats and contraindications associated with these results, as discussed below.

1) Specific tumor subtypes of cancer patients and follow-up time of clinical studies display different responses to dietary interventions. For example, a prospective cohort study involving 335,054 female participants shows that a high vegetable intake is correlated with a lower risk of hormone-receptor-negative breast cancer (Emaus et al., 2016). However, a 11 to 20-year follow-up study found that high fruit and vegetable consumption is not associated with the overall risk of breast cancer (Jung et al., 2013). Additionally, certain ingredients in the diet play multiple roles in improving the adverse symptoms of cancer patients, while have some oncogenic risks. Capsaicin, the major active ingredient of pepper, has been reported to improve
appetite loss, promote heart function, relieve pain and inhibit tumor proliferation (Diaz-Laviada and Rodriguez-Henche, 2014; Clark and Lee, 2016; Friedman et al., 2018). On the other hand, a recent study has shown that spicy diets increases the occurrence risk of esophageal squamous cell carcinoma (Yang et al., 2020). Therefore, additional attention should be given to various nutritional components in the diet and their potential side effects. Distinct scientific diet management and personalized diet recipes should be formulated for patients with specific types of cancer.

2) Although several accumulated studies have shown that exercise interventions improve the prognosis and is associated with a reduction in cancer risk, the role of exercise in the treatment of specific types and stages of cancer remains unclear (Hojman et al., 2018). Furthermore, many cancer patients may not be able to adapt to the high intensity and the duration of long duration exercise, and this will lead to an eventual failure in exercise intervention (Campbell et al., 2012). Thus, a personalized workout regimen with specific type, intensity, and duration of exercise should be better developed by professionals in order to provide more effective choices for cancer patients.

3) Some traditional medicines for improving chronic stress-related adverse symptoms also contribute to tumor progression and/or cause other side effects. For example, melatonin improves sleep disorders of cancer patients, but long-term use of melatonin may disrupt the homeostasis of endogenous hormone secretion and result in drug dependence or tolerance. Moreover, for many cancer patients, fluoxetine plays a critical role in relieving depression, but it also causes insomnia and anxiety in some of them (Wernicke, 2004). In addition, despite the widespread use of morphine to alleviate pain in advanced cancer patients, morphine also promotes cancer metastasis and enhances cancer stem-like phenotypes (Niu et al., 2015). Hence, comprehensive clinical trials and prospective studies should be conducted to improve the safety and effectiveness of traditional and alternative medicine for relieving chronic stress-induced adverse symptoms.

4. Traditional Chinese medicine
Traditional medicine originated from diverse cultural backgrounds plays an integral role in anti-tumor treatment, such as yoga therapy, massage therapy, moxibustion treatment and traditional Chinese medicine (TCM). For example, a meta-analysis including 2166 breast cancer patients demonstrates that yoga therapy is effective in improving health-related quality of life and reducing cancer-related fatigue and sleep disturbances (Cramer et al., 2017). Another randomized early phase trial including 66 female breast cancer survivors shows that weekly Swedish massage therapy produces clinically significant relief of cancer-related fatigue (Kinkead et al., 2018). Moreover, several clinical trials reveal that moxibustion therapy is an efficient supportive cancer care in relieving fatigue, nausea and vomiting (Lee et al., 2010, Kim et al., 2017). Here we mainly review the critical roles of TCM, including acupuncture, Chinese herbal medicine and Tai Chi in cancer therapy and relieving adverse symptoms. Yin Yang as its theoretical basis of TCM, which holds that an imbalance in Yin Yang in the human body leads to diseases. The practice of TCM contains a variety of treatment approaches, such as acupuncture, Chinese herbal medicine and Tai Chi. Previous studies indicate that TCM alleviates chronic stress caused by cancer pain and reduces psychological distress in cancer patients, thereby limiting cancer progression (Liu et al., 2017; Sun et al., 2018; Dang et al., 2019).

4.1 Acupuncture and acupressure

Acupuncture and acupressure are now widely used as an adjuvant treatment in cancer therapy (O'Regan and Filshie, 2010). A portion of cancer patients suffering from moderate to severe pain can not achieve adequate pain remission (van den Beukven-van Everdingen et al., 2007). Acupuncture is effective in controlling various types of cancer-related discomfort, including terminal cancer pain, postoperative pain and aromatase inhibitor-induced arthralgia. For example, a 6-week randomized, double-blind, controlled trial involving 30 advanced cancer patients shows that intradermal acupuncture is a feasible and safe treatment for ameliorating pain (Kim and Lee, 2018). Another meta-analysis of existing randomized clinical trials confirms that acupuncture and acupressure alleviate postsurgical pain and reduce the use of opioid analgesics in cancer patients (He et al., 2019). Furthermore, arthralgia caused
by aromatase inhibitors is a common side effect of hormone therapy in breast cancer patients. Acupuncture acts as an effective non-pharmacologic treatment strategy that relieve aromatase inhibitor-induced joint pain in breast cancer patients (Chen et al., 2017). On the other hand, acupuncture also improves life quality of cancer patients. For example, combination of acupuncture and usual care intervention for breast cancer patients improve self-reported fatigue and overall quality of life (Molassiotis et al., 2012). Acupuncture also ameliorates hot flash symptoms and depression in cancer patients (Haddad and Palesh, 2014; Lesi et al., 2016). A recent meta-analysis shows that acupuncture has reliable effects on improving agonal breathing (the gasping for air) in middle- and end-stage cancer patients (von Trott et al., 2020). Some patients do not respond well to acupuncture treatment. A meta-analysis demonstrates that acupuncture cannot alleviate depressive symptoms of cancer patients (Tao et al., 2015). Another study on the relationship between acupuncture therapy and disease-specific life quality indicates that additional acupuncture treatment over 6 months during chemotherapy does not improve the quality of life in patients with breast cancer (Brinkhaus et al., 2019). Furthermore, a recent study reveals that electroacupuncture (ES) diverse sympathetic pathways in a somatotopic-, time- and intensity-dependent manners. This leads to activation of distinct adrenergic receptors (ARs) to produce either anti-inflammatory or pro-inflammatory effects (Liu et al., 2020). The differential somatotopic organization and intensity dependence in diverse autonomic pathways could explain variable effects on relieving adverse symptoms. This is particularly true if different stimulation intensities and/or acupoints are used in different cancer patients. As acupoint can selectively drive specific somatosensory autonomic pathways, it could form a modern basis for linking somatic tissue stimulation to modulation of internal organ physiology. As such, future studies on mapping somatosensory pathways to distinct autonomic pathways may optimize stimulation parameters, enhance clinical practice and improve both the efficacy and safety in using acupuncture as a treatment for cancer patients.

4.2 Chinese herbal medicine

With advances in TCM during recent years, Chinese herbal medicine
preparations have become an integral part of complementary anti-tumor therapies. For example, curcumin inhibits breast cancer cell proliferation and migration through activation of the 5' AMP-activated protein kinase (AMPK) pathway (Guan et al., 2016). In vitro, *Taxus chinensis* reverses cisplatin resistance in lung cancer stem cells (Jiang et al., 2016). In a subcutaneous mouse cancer model, epigallocatechin gallate shows a significant inhibitory effect on non-small cell lung cancer progression and angiogenesis (Sakamoto et al., 2013). A 4-year double-blind, randomized placebo-controlled trial confirms that daily intake of 300 mg of berberine reduces risk of recurrence in patients with a history of colorectal cancer (Chen et al., 2020). In addition, recent studies also show that Chinese herbal medicine plays vital roles in relieving several adverse symptoms of cancer patients. Levo-corydalmine, an alkaloid isolated from a Chinese herb, significantly alleviates cancer pain-induced hypersensitivity by inhibiting tumor necrosis factor-α and IL-1β expression (Hu et al., 2017). According to a meta-analysis of 18 randomized controlled trials, a variety of proprietary Chinese medicine and Chinese herbal medicines, including the Shugan Jieyu capsule and Xiao Yao decoction, relieves depressive symptoms in cancer patients (Li et al., 2019).

An important issue with many herbal medicines is that the active ingredient is often unknown and the quality of these ingredients may well differ depending on where the herbs are grown. This may be related to some reports of Chinese herbal medicines multiple side effects. Examples include, aristolochic acid related renal impairment (Gokmen et al., 2013) and hepatotoxicity caused by *Polygonum multiflorum* (Meng et al., 2017). This is likely due to the complex components and unclear therapeutic targets. For example, a recent study demonstrates that aristolochic acid significantly drives somatic mutation accumulation and macroscopic clonal expansions in morphologically normal human urothelium, which plays a vital role in bladder cancer onset and evolution (Li et al., 2020). Paclitaxel, the effective component of *Taxus chinensis*, may cause sensory dysfunction and pain characterized by preferential impairment of myelinated fiber function in cancer patients (Dougherty et al., 2004). Furthermore, the combination of Chinese herbal medicine and
chemotherapy may increase the risk of adverse reactions. For example, a case report shows that artesunate and Huanglian decoction used as complements control tumor progression, but this combination leads to an abnormal elevation of liver enzymes and deterioration of clinical status in a glioblastoma multiforme patient treated with temozolomide following surgery (Efferth et al., 2017). Hepatotoxicity is very rare in artesunate and *Coptis chinensis* treatment, and *Coptis chinensis* even exhibits protective effects on the liver (Jansen et al., 2011; Choi et al., 2013). These findings indicate that Chinese herbal medicine may alter the original targets when used in combination with other drugs. As such, the major effective components should be purified and the specific mechanisms of Chinese herbal therapy should be further identified during anti-tumor treatment.

**4.3 Tai Chi**

Tai Chi not only strengthens the body and improves balance but also affects numerous chronic diseases, especially cancer. A clinical trial involving 166 prostate cancer patients showed that Tai Chi relieves cancer-related fatigue and improves quality of life (Kinney et al., 2019). Tai Chi also reduces insomnia and depressive symptoms as assessed in 145 breast cancer patients (Irwin et al., 2017). This same group has shown that Tai Chi very effectively improves the efficacy of the immune response to varicella-zoster virus in older adults, thereby reducing the risk of contracting shingles (Irwin et al., 2007). Furthermore, due to its gentle movement, Tai Chi can avoid aggravating the cardiopulmonary burden and eliminate the symptoms of tension and anxiety. Thus, Tai Chi is especially suitable for specific patients, namely elderly, or patients with advanced cancer.

Of note, several meta-analyses indicate that Tai Chi has little effect on improving physical health, social or emotional well-being and life quality in breast cancer patients (Yan et al., 2014; Pan et al., 2015). Moreover, the therapeutic effects of Tai Chi are usually evaluated by self-reports of patients rather than the standard substantive evidence. This may limit clinical application. Therefore, additional high quality randomized controlled trials should be performed to provide more reliable evidence for the role of Tai Chi in specific populations of cancer patients, which will
be important for the global adoption of personalized medicine.

V Conclusions

In this review, we discuss how chronic stress affects specific hormones that regulate downstream targets through the HPA axis and SNS. This contributes to a variety of events that are critical for the initiation and progression of cancers, including proliferation, genomic instability, angiogenesis, metastasis, immunosuppression and metabolic disorders. Furthermore, emerging studies have revealed that chronic stress dysregulates circadian rhythms and gut microbiota composition. As circadian rhythm disorders and gut dysbiosis exhibit important roles in tumorigenesis, the underlying mechanisms of their disruption by chronic stress needs to be better understood. These findings also provide the basis for the diagnosis and therapy of stress-associated tumor malignancies.

Chronic stress activates ADRBs to stimulate downstream signaling pathways that are mainly responsible for activation of several essential oncogenes that lead to tumor development. Evaluation of stress status and detection of related hormones in plasma provides a strategy for clinical cancer prognosis and treatment. Furthermore, accumulating evidence suggests that numerous ADRB blockers possess anti-tumor properties in a variety of oncologic malignancies. The non-selective ADRB antagonist propranolol is widely applied in clinical treatment due to its relatively low toxicity and minimal side effects. This suggests that propranolol might be used to reverse the negative effects of chronic stress on cancer progression in the clinic. Moreover, the selective ADRB2-specific antagonist ICI118,551 was reported to suppress stress-induced carcinogenesis in several mouse models, but it has not been approved for clinical application. More in-depth studies concerning how chronic stress promotes cancer progression, and particularly the combination of ADRB blockage and downstream molecular inhibitors, will provide a new orientation for cancer therapy. In addition to inhibition of chronic stress-induced downstream signaling, psychological interventions such as CBSM intervention and psychotherapy effectively relieve chronic stress in cancer patients. These intervention methods enrich our understanding of the importance of humanistic care for cancer patients. Specialized
psychotherapists are needed to evaluate and manage the physical and emotional
disruptions of cancer patients, both of which might attenuate the oncogenic effects of
chronic stress. Finally, TCM, including acupuncture and acupressure, Chinese herbal
medicine and Tai Chi are often applied for pain relief and depression remission of
cancer patients. Recent studies suggest that TCM exhibits a role in tumor suppression.
As TCM has few adverse side effects and represents widespread feasibility, a
combination of current therapeutic strategies with TCM should be more carefully
explored.
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Conflict of Interest
The authors of this manuscript declare no competing interests.

**Figure Legends**

**Fig. 1. Chronic stress-induced hormones affect important oncologic events.**

Chronic stress increases secretion of epinephrine, norepinephrine, glucocorticoids, prolactin and oxytocin but reduces dopamine. Prolactin (PL) is synthesized in the adenohypophysis and ultimately promotes breast cancer tumor metastasis. Dopamine (DA) is a neurotransmitter released from the hypothalamus that is transported via the median eminence to the adenohypophysis to inhibit prolactin release. Dopamine is the immediate precursor of norepinephrine synthesis and also impairs angiogenesis and tumor proliferation. Oxytocin (OT) is synthesized in the hypothalamus and released from posterior pituitary neurons directly into the blood. It has been shown to promote metastasis but also to suppress tumor proliferation *in vitro*. Chronic stress is well known to activate the hypothalamic-pituitary axis (HPA) by acting on the hypothalamus to produce corticotropin-releasing hormone (CRH). Corticotropin-releasing hormone is delivered to the adenohypophysis via the median eminence where it stimulates secretion of adrenocorticotropic hormone (ACTH). Following release into the blood, ACTH acts on the adrenal gland to release mostly epinephrine but also norepinephrine from the medulla and glucocorticoid hormones from the cortex. Importantly, chronic stress activates the sympathetic nervous system (SNS) to release norepinephrine that acts locally on many organs as a neurotransmitter. Both catecholamines and glucocorticoid hormones promote tumor proliferation, metastasis, angiogenesis and stem-like traits of cancer cells. Part of the elements in this figure are cited from https://smart.servier.com/. The link of license is as follows: https://creativecommons.org/licenses/by/3.0/deed.en.
Fig. 2. Biological mechanisms underlying chronic stress-induced cancer progression.

Chronic stress activates ADRBs, the PKA/VDCC/IGF axis and AMPK signaling pathways to promote cancer cell proliferation. Chronic stress leads to cancer chromosomal instability and DNA damage through activation of Gs-PKA/β-arrestin and suppression of p53. Furthermore, chronic stress promotes angiogenesis through activation of the cAMP/PKA signaling pathway, elevating VEGF expression. Chronic stress promotes cancer metastasis by increasing expression of TGF-β, IL-6 and PTGS2, activating the CCL2/CCR2 axis and triggering the ERK-VEGF/MMP2 pathway. In addition, chronic stress causes immune evasion through increasing the number of M2 macrophages and decreasing CD8^+ T cells and IFN-γ release. Chronic stress also promotes tumor progression by inducing metabolic disorders such as ACACA- and ACLY-mediated lipid synthesis and HK2- and LDHA-regulated glycolysis.

Abbreviation. ADRBs: β-adrenergic receptors; PKA: protein kinase A; VDCC: voltage-dependent calcium channels; IGF2: insulin like growth factor 2; IGF-1R: insulin like growth factor 1 receptor; AMPK: adenosine monophosphate-activated protein kinase; Gs: guanyl nucleotide regulatory proteins; cAMP: cyclic adenosine monophosphate; VEGF: vascular endothelial growth factor; CCL2: C-C motif chemokine ligand 2; CCLR2: C-C motif chemokine receptor 2; TGF-β: transforming growth factor-β; IL-6: interleukin 6; PTGS2: prostaglandin-endoperoxide synthase 2; ERK: extracellular regulated MAP kinase; MMP2: matrix metalloproteinase 2; IFN-γ: interferon-γ; HK2: hexokinase 2; LDHA: lactate dehydrogenase A; ACLY: ATP citrate lyase; ACACA: acetyl-CoA carboxylase alpha. Part of the elements in this figure are cited from https://smart.servier.com/. The link of license is as follows: https://creativecommons.org/licenses/by/3.0/deed.en.
Fig. 3. Interventions that reduce cancer promotion caused by chronic stress.

Several possibilities exist to reduce the detrimental effects of chronic stress on promotion of cancer. They are divided into four categories: pharmacologic blockade of β-adrenergic receptors, inhibitors of specific targets, psychosomatic behavioral interventions and Traditional Chinese medicine. Both non-selective β-adrenergic blockers and β2-specific blockers inhibit chronic stress-promoted cancer progression. The combination of β-adrenergic blockers and specific inhibitors exhibits more efficacious anti-tumor responses. In mice, inhibition of specific targets suppresses chronic stress-induced tumor promotion, such as protein inhibitors (NKCC1 targeting inhibitor bumetanide), metabolic targeting drugs (LDHA specific inhibitor vitamin C) and gene ablation (arrb1-knockout and tsc22dd3 deletion). Furthermore, psychosomatic behavioral interventions such as diet interventions, aerobic exercise program and psychotherapy can be applied to relieve chronic stress. In addition, traditional Chinese medicine including acupuncture therapy, Chinese herbal medicine and Tai Chi serve as potential therapeutic strategies for dealing with chronic stress-induced cancer progression. Part of the images in this figure are cited from https://smart.servier.com/. The link of license is as follows: https://creativecommons.org/licenses/by/3.0/deed.en.

Highlights

1. Regulation of chronic stress-induced hormones in cancer;
2. Mechanisms that link chronic stress to cancer;
3. Therapy for chronic stress-induced tumor progression.