Mechanisms underlying the effects of stress on tumorigenesis and metastasis (Review)

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Abstract. Stress is one of the fundamental survival mechanisms in nature. Although chronic or long-lasting stress can be detrimental to health, acute or short-term stress can have health benefits. The aim of the present review was to address the complexity and significance of stress in tumorigenesis. The review covers an evaluation of previously used and reported experimental animal models of stress, as well as the effects of stress on the neuroendocrine system, immune function, gut microbiota, and inflammation and multidrug resistance, all of which are closely associated with cancer occurrence, progression and treatment. The review concludes that understanding the efficacy of stress management (prevention and rehabilitation) is crucial to the development of comprehensive and individualized strategies for cancer prevention and treatment.

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1. Introduction

Stress is a constellation of events that begins with a stressor, leading to stress perception and subsequently resulting in stress response (1). Stress can impair the balance or homeostatic state of an organism physiologically or psychologically

when exposed to extrinsic or intrinsic adverse forces (2). It is well known that stress is ubiquitous and unavoidable in life. For certain individuals, stress can serve as a stimulant under certain conditions and as a burden under others. In addition, stress serving as a stimulant in certain individuals may be a burden for others, which indicates that there exists a varying degree of stress susceptibility among individuals (3,4). Stress occurs when an organism perceives a disruption, or a threat of disruption, of homeostasis. Factors that can induce stress include, among others, social circumstances, physical environment, hypoxia, emotional state, pain, glucose deprivation, accidents and chronic anxiety (5). Stress-related symptoms include negative emotions or altered mood and behavior, such as anxiety, irritability, anger, startle response, hostility and depression, which can negatively affect various organs of the human body (6). Studies have preliminarily revealed that differences in the stress experienced by different individuals can be due to genetic and environmental factors (7,8). It is also generally believed that moderate stress, such as routine or regular exercise or physical activity, can enhance the body's immune response and reduce the risk of cancer occurrence, progression and mortality (9,10), while chronic stress can affect a number of physiological functions and lead to several diseases, including cancer (11-13) (Table I). Stressors can result in mood and anxiety disorders, including depression, anxiety and irritability, which may be associated with malignancies (14,15).

In order to elucidate the underlying mechanisms linking stress with tumorigenesis and metastasis, it is necessary to establish effective animal models. At present, the most common animal stress models are those developed for chronic restraint stress, maternal separation, and dietary and environmental stress. Tumor metastasis is a complex process that consists of proliferation/angiogenesis, detachment/invasion, embolism/circulation and evasion of immune system surveillance. The present review attempted to classify and summarize the mechanisms underlying the role of stress in tumorigenesis and cancer progression.

2. Stress and animal models of stress

Animal models mimicking the pattern of human diseases serve a key role in understanding the effects of stress on cancer. To study this effect, multiple physiological stress models have been

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utilized to promote fear or anxiety in rodents, including the following: i) Social isolation model, where laboratory rodents, which are highly social creatures, are housed individually in cages for extended periods to elicit loneliness; ii) restraint stress model, in which the animals are immobilized or confined to small spaces; and iii) intimidation-induced stress model, which involves placing rodents into the cage of another animal. When categorized by type, stressors are classified as physical (trauma/injury and exercise/exhaustion), cognitive (anxiety and depression), a combination of physical and cognitive (fire-fighting on a 24-h shift) or chemical (environmental toxins and diet). When categorized by duration, stressors are classified as acute (minutes to hours), and chronic (months to years) (16,17).

At present, the chronic mild stress (CMS) model is one of the most widely used stress models, allowing for a combination of a large variety of stressors with different numbers/lengths of intervals and the measurement of different behaviors as a response to rewards (18). Specifically, the CMS model consists of immobilization, forced swimming, noise, hypothermia, social isolation, resident/intruder aggression, maternal deprivation, stroboscopic illumination, cage titling, and food, water or sleep deprivation (19). Meanwhile, the chronic restraint stress animal model is one of the most common immobilizations, in which the duration of restraint has ranged from 1 to 12 h daily (20,21). Generally speaking, these stress models are evaluated based on three major criteria: i) Construct validity, where the experimental conditions are replicating causes of human diseases; ii) face validity, where the symptoms observed in diseased animals are consistent with clinical observations; and iii) predictive validity, where the animal responds to the treatment currently used in the clinic (22). However, no studies have systematically evaluated the validity or the efficiency of the CMS model, as researchers have often chosen a particular combination of stressors with timing based on previous practical experience and/or the particular requirements of their experiments (18). Stress can be harmful when it is chronic or long lasting, but a fact that is often overlooked is that a stress response can have salubrious adaptive effects in the short run, and that short-term stress may enhance cellular immunity and increase early resistance to cancer (23,24). The timing or duration of the stress models is an important factor that requires consideration. Therefore, it is essential to distinguish between acute and chronic stress in the following discussion (Fig. 1).

3. Mechanisms underlying the effects of stress on tumorigenesis and metastasis

Effects of stress on the neuroendocrine system. In the fast-paced society of today, the pressure on individuals is high, and it often manifests itself in the form of anxiety, tension, insomnia and depression, all of which can lead to chronic stress. The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) are the two branches of the neuroendocrine system that govern the response to stress (25,26). Corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), released from the hypothalamus, can activate the pituitary gland to release adrenocorticotropic hormone (ACTH), encephalin and endorphin (END), and the adrenal cortex to release ACTH-induced glucocorticoid (GC) (3,27). The release of CRH

is under excitatory input from the amygdala and inhibitory input from the hippocampus (28). Meanwhile, the secretion of CRH and AVP is characterized by a precise circadian rhythm that can be disrupted by imposed stressors, and a circadian rhythm disorder can have the same detrimental effects as chronic stress (29,30). Stress can also result in increased secretion of catecholamines, including norepinephrine (NE) and epinephrine (E), which can enhance alertness and physiological functions, and elicit the fight-or-flight response (31,32). GC serves an important role in the treatment and chemo-resistance of tumors, and catecholamine can promote tumor growth and metastasis (33,34). Adolescent chronic stress can cause HPA hypo-responsiveness and depression-like behavior (35). Psychosocial stressors in cancer can result in the dysregulation of the HPA axis, and vice versa (36). Restraint stress facilitates cancer angiogenesis and metastasis by releasing β-END, prolactin, increasing concentrations of circulating catecholamine and GC, and increasing tumor-associated macrophage infiltration into the primary tumor (37,38). Psychological stress may attenuate antiangiogenic therapy, primarily through activating β-adrenergic signaling to promote tumor angiogenesis (39), and β-blockers or behavioral therapies can limit skeletal metastasis of breast cancer cells (40). Dopamine (DA) is also a catecholamine hormone, which can stabilize tumor blood vessels to block the effects of chronic stress on tumor vasculature, as the depletion of DA under chronic stress conditions creates a permissive microenvironment for tumor growth (41,42). Notably, studies have revealed that DA acts through five types of DA receptors; DA type-1 receptor overexpression is associated with advanced breast cancer and a poor prognosis (43), but DA type-2 receptor has been found to inhibit tumor growth (44).

Furthermore, since the lymphatic system and the pancreas are innervated by fibers of the SNS and have receptors for SNS neurotransmitters, chronic stress-induced SNS activity can increase pancreatic cancer growth, lymphatic vessel contraction and lymphocyte output into the lymphatic circulation. These processes may affect tumor lymphatic dissemination and cancer progression (45,46). Chronic restraint stress can attenuate the levels and function of p53 proteins, and promote the growth of human xenograft tumors, which is mediated by GC elevation during chronic restraint stress (47). A study has shown that exposure to chronic psychological stress may lead to significant changes in the proteomic profile of tumors (48). It is noteworthy that cytokines are potent activators of the central stress response and have regulatory effects on the HPA axis by forming a feedback loop through which the immune/inflammatory system communicates with the brain (49). The duration and magnitude of stress-induced increases in NE, Epi and GC have significant effects on immune cell redistribution and function (50,51) (Fig. 2). However, several studies have indicated that β-adrenergic receptor blockers can reverse the effects of chronic stress on cancer progression and abrogate drug resistance, which merits further investigation as a novel strategy for cancer treatment (52-54).

Effects of stress on immune function. Stress exerts pleiotropic effects on the immune system, affecting the innate and adaptive immune responses (55). Stress-induced immune responses can be categorized as immune-protective, immune-pathological and immune-inhibitory. Notably, stress can be categorised as good or bad, based on the duration of

Table I. Differences between acute stress and chronic stress.

Differences	Chronic stress	Acute stress	(Ref.)
Duration	Prolonged-term (months to years)	Short-term (minutes to hours)	(16,17)
Intensity	Strong/weak intensity stimulation	Strong intensity stimulation	(1,2,8,9,12)
Animal models	Social isolation, chronic mild stress, intimidation	Electric shock, immobilization	(19,20,21)
Response system(s)	Mainly activates the HPA axis	Activates the HPA axis and the sympathetic neural system	(5,25,26,31,32)
Origin	Adrenal medulla	Adrenal medulla and sympathetic ganglia	(5,27,28,45,46)
Response outcomes	Elevations in catecholamines, i.e., epinephrine and norepinephrine	Elevations in catecholamines and glucocorticoids	(5,25-28)
Immune response	Immune suppression/ immune pathology	Immune protection/immune pathology	(56,57,59-62)
Possible significance	Detrimental	Beneficial	(9,10,11,13)
Tumor	Tumor development and progression	Inhibits tumor development and progression	(11-13,24-26)

HPA, hypothalamic-pituitary-adrenal.

the biological stress response (11). It is well known that acute stress can enhance immune function, whereas chronic stress can suppress it, as well as increasing the susceptibility to cancer (1). Stress can have beneficial and harmful effects, depending on the type of immune response; factors that determine the effects of stress on immune function include duration (acute or chronic), endogenous versus synthetic GCs and time of stressor (at early stages or late stages of the immune response) (1,56) (Fig. 1). It has been reported that chronic stress can affect individual components of the cellular immune system and downregulate the cellular immune response (57,58), which manifests in the form of a significant decrease in body weight and lymphatic organs (spleen, thymus and axillary lymph nodes) and a significant increase in the apoptotic cell count in all lymphatic organs (59). Chronic stress may influence the immune function and promote tumor growth by depressing T-cell-mediated immunity and reducing the lymphocyte count, which may depend on toll-like receptor 9 and β-arrestin 2 (60,61). Cytotoxic T lymphocytes (CTLs) are capable of secreting cytokines, such as interferon-γ (IFN-γ), and other effector molecules that serve a role in immune surveillance against tumor cells and the eradication of cancer stem cells (62), but NE and GC can decrease the number of CTLs or impair their function to attenuate their antitumor effect (63). However, a previous study found that psychological stress could augment immune response (64). With regards to the effect on non-specific cellular immunity, previous studies have demonstrated that chronic stress can weaken natural killer (NK) cell function and inhibit their activity, promoting tumor progression (65). Stress can also stimulate macrophages or monocytes to secrete interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α, but reduce the secretion of IL-2, IFN-γ and major histocompatibility complex (MHC), which may aid tumor cells to evade immune surveillance (66,67). Tumor associated-macrophages (TAMs) are one of the components of the tumor microenvironment in which stress can increase tumor infiltration by macrophages,

and macrophage infiltration can mediate stress-enhanced metastasis in primary breast cancer (68). GC can induce macrophage phenotype changes from M1 to M2 to promote tumor progression (69). Daily restraint stress can also lead to increased monocyte chemoattractant protein-1 (MCP-1) expression and infiltration of cluster of differentiation (CD)14+ and CD68+ cells. In addition, the elevation of peripheral blood monocytes and TAMs has been associated with a worse progression-free survival time in patients with ovarian cancer (70). The matricellular protein thrombospondin-1 response to stress via the cluster of differentiation 47 (CD47) and thrombospondin-1/CD47 signaling pathways serves an important role in tumor angiogenesis (71). The upregulated CD47 protein on the surface of cancer cells can combine with signal regulatory protein-α, located on the surface of macrophages, in order to avoid phagocytosis. The expression of β2-microglobulin (a component of MHC class I molecules) in cancer cells directly protects them from phagocytosis, which is mediated by the inhibitory receptor leukocyte immunoglobulin-like receptor B1, whose expression is upregulated on the surface of macrophages (72). Dendritic cells (DCs) are specialized antigen-presenting cells that have a direct cytotoxic effect on tumor cells (73), but restraint stress compromises the suppressor function of regulatory T cells (Tregs) and alters DCs to contribute to intestinal inflammation (74). A short-term, stress-induced increase in IFN-γ, macrophage inflammatory protein-3α, TNF-α, MCP-1, IL-1α, IL-1β and IL-6 can enhance the immunization phase of cell-mediated immunity (75,76). Nevertheless, chronic stress can lead to a reduction in the number of cytokines, including IFN-γ, IL-2 and IL-12, due to the inhibitory effect of GC, NE and E, which have an important antitumor function (77,78). Chronic stress-induced neuroendocrine changes have been found to suppress the immune response, including NK cell cytotoxicity, phagocytosis, inflammatory cytokine production and cytotoxic T-cell activity, compromising the most important effectors of the immune response against tumors (66). It is
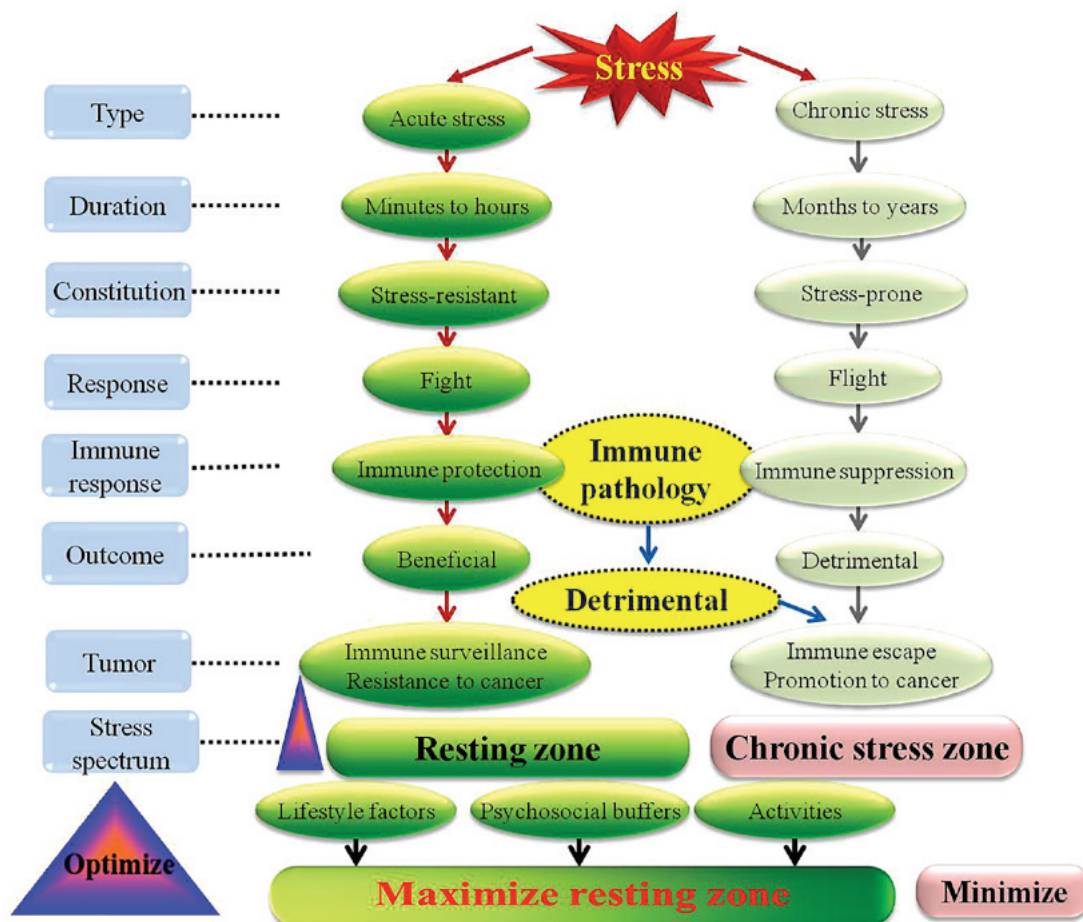
Figure 1. Types of stress and their effects on immune function. Stress can be categorized as either chronic or acute, based on its effects on the body and its duration. Certain individuals are more prone to stress, while others more resistant; this is due to constitution-associated differences among individuals. The fight-or-flight stress response is one of the fundamental defense mechanisms in nature that enables the body to survive. Acute stress can serve an important role in the 'fight' response by exerting immune protection functions, which can prove beneficial to the body and strengthen immune surveillance and resistance to cancer. Chronic stress, on the other hand, can serve an important role in the 'fight' response, which is detrimental to the body and may lead to immune suppression or immune escape, as well as promote cancer. It is worth noting that acute stress may also lead to immunopathology when it is experienced during self/innocuous antigen/allergen exposure, which can result in the increase of pro-inflammatory cytokines and is harmful to the body. According to the afore-mentioned model, there exists a resting zone between chronic (harmful) and acute (beneficial) stress, and the extent and efficiency with which an organism returns to its resting zone following stress depends on its resilience. Certain factors, such as lifestyle, psychosocial buffers and activities, can maximize the resting zone by optimizing beneficial stress and minimizing harmful stress, which enables the body to stay on the positive side of the stress spectrum.

worth highlighting that, as the largest organ and the body's first line of defence, cutaneous cell-mediated immunity serves an important role in the elimination of immune-responsive tumors such as squamous cell carcinoma (24). Short-term stress not only enhances primary cutaneous immune responses, but also augments secondary or recall responses in the skin (79). In addition, the lymphatic system serves an important role in immune function, while also contributing to tumor cell invasion and metastasis. Studies have found that chronic stress can promote tumor cell dissemination by remodeling the lymph vasculature (80,81).

Effects of stress on the gut microbiota. The gut microbiota serves an important role in maintaining gut homeostasis (82). The most common bacterial phyla in the gut include the Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria, and the composition of the gut microbiota is highly sensitive to chronic stress (83,84). Furthermore, stress during the perinatal period can markedly influence the microbiota, leading to long-lasting immunological aberrations (85). It has been demonstrated that microbiota dysbiosis is closely associated with the occurrence, development and treatment of cancer (86,87). Certain bioactive substances of the microbiota metabolite production have also been found to be involved in carcinogenesis (88). The influence of the gut microbiota on tumorigenesis and development is mainly through several methods that include direct contact with the tumor (89), affecting the tumor cells by regulating body metabolism indirectly (90,91) and promoting tumor progression by regulating the immune system (92,93). Studies performed on a restraint stress mouse model suggested that commensal microbiota can affect the postnatal development of the HPA stress response (94), and that gut dysbiosis is associated with brain dysfunction and stress-related behavior, including anxiety and depression (95,96). It was shown that the absence of the gut microbiota enhanced anxiety-like behavior and neuroendocrine response to acute stress in rats (97). Chronic stress can not only cause an imbalance in and disorders of the gut microbiota, but also behavioral, cognitive and biochemical aberrations, which may be involved in the microbiota-gut-brain axis. A study revealed that *Lactobacillus helveticus* NS8
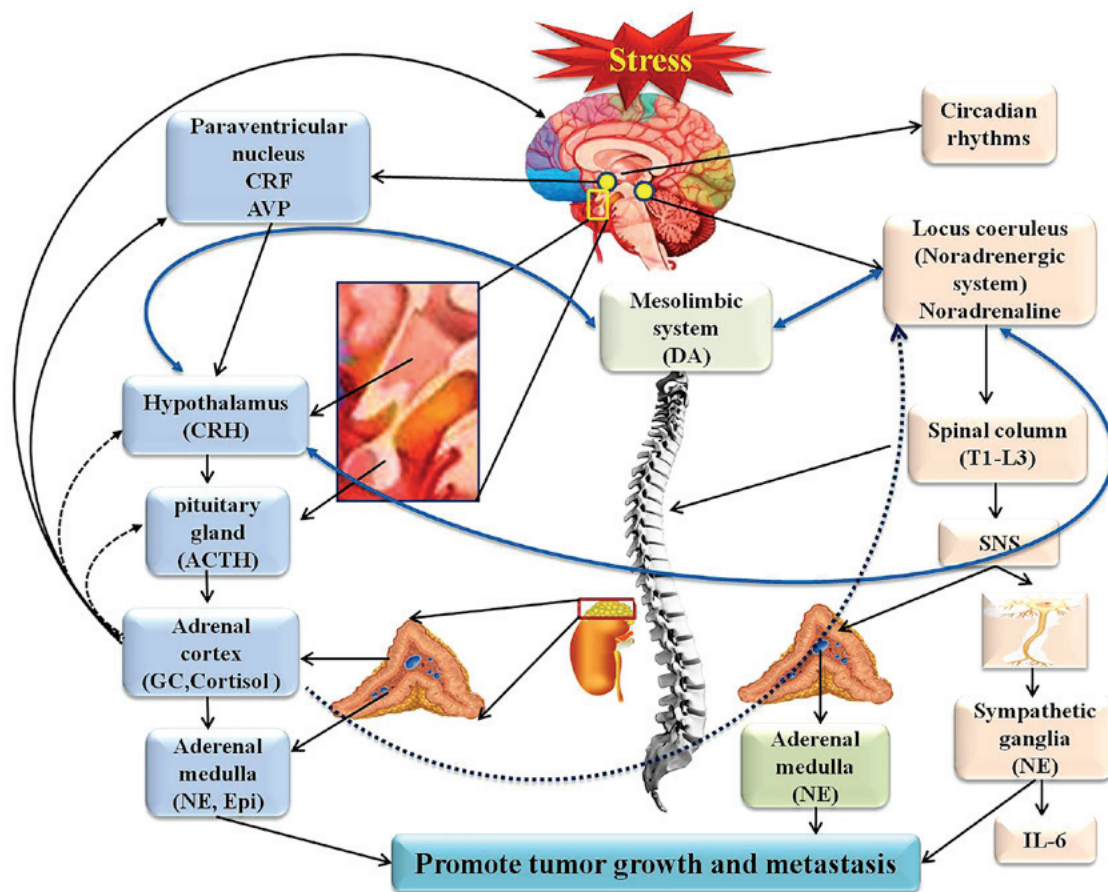
Figure 2. Systemic effects of stress on the neuroendocrine system. The HPA axis and the SNS are the two key branches of the neuroendocrine system that govern the response of an organism to stress. In response to stress, the paraventricular nucleus of the hypothalamus secretes CRH and AVP, which cause the pituitary gland to secrete ACTH. Meanwhile, the CRH/AVP neurons and central catecholaminergic neurons of the locus coeruleus/NE system are reciprocally innervated and activated. The secretion of CRH and AVP is characterized by a precise circadian rhythm. Subsequently, ACTH stimulates the adrenal cortex to release GC and cortisol. In addition, the HPA axis is controlled by feedback loops that tend to normalize the time-integrated secretion of cortisol. The SNS originates in the brain stem, with the sympathetic nerves located between the intermediolateral column of the T1 and L3 vertebrae. From there, cells synapse with post-synaptic ganglia located in the sympathetic trunk or in splanchnic ganglia throughout the body, and ultimately release NE. Under the condition of stress, particularly chronic stress, NE can promote tumor growth and metastasis. In the image, solid lines indicate stimulation and dashed lines indicate inhibition. HPA, hypothalamic-pituitary-adrenal; SNS, sympathetic nervous system; CRH, corticotrophin-releasing hormone; CRF, corticotrophin releasing factor; AVP, arginine vasopressin; ACTH, adrenocorticotropic hormone; IL-6, interleukin-6; NE, norepinephrine; Epi, epinephrine; GC, glucocorticoid; DA, dopamine.

can improve chronic restraint stress-induced behavioral and cognitive dysfunction (98). Rifaximin can alter the bacterial population in the ileum of rats and lead to a relative abundance of *Lactobacillus*, which can prevent intestinal abnormalities and visceral hyperalgesia in response to chronic psychological stress (99). A study showed that probiotic treatment attenuated the HPA response to acute stress (100). Notably, a recent study demonstrated that dietary bioactive compounds and probiotics could reduce the risk of colon cancer by shaping functional gut microbiota (101). In addition, resident gut bacteria can affect patient response to cancer immunotherapy, and maintaining a healthy gut flora could assist patients in their fight against cancer (102). Based on the aforementioned literature, we tentatively conclude that there may be an association of mutual causality between tumorigenesis and gut microbiota imbalance.

Effects of stress on inflammation. Approximately 25% of all cancer types are associated with chronic inflammations of broad origin (103). Just as stress can be divided into acute and chronic according to its beneficial or detrimental effects on the body, so can inflammation. It has been shown that chronic

inflammatory processes affect all stages of tumor development, as well as the efficacy of therapy, particularly in gastric, hepatic and colorectal cancer (104,105). There are two major signaling pathways underlying cancer-related inflammation: The transcription factor nuclear factor-κB (NF-κB) and the signal transducer and activator of transcription 3 signaling pathways, which can be activated by the majority of cancer risk factors, including stress, diet, infectious agents and environmental pollutants (106). Studies have also revealed that inflammatory cells can be recruited by stress to tumor sites, increasing the formation of blood vessels (107). Meanwhile, stress-inducible inflammatory factors and genes, including IL-6, IL-8 and vascular endothelial growth factor, are increased in the circulation following stressor exposure. Stress can lead to metastatic invasion and metabolic syndrome by the activation of the HPA axis and SNS, respectively, which are characterized by an increased production of IL-6, TNF-α, llasminogen activator inhibitor-1 and metalloproteinase-2 and -9 (108). Reciprocally, adipose-derived IL-6 may further stimulate the HPA axis, forming a deleterious vicious cycle (109). Chronic psychological stress can induce vascular inflammation via the TNF-α

and p38/c-Jun N-terminal kinase pathways and increase the expression of inflammatory molecules, including mRNA and proteins such as TNF-α, C-reactive protein, MCP-1, macrophage migration inhibitory factor and intercellular adhesion molecule-1 (110). Psychological stress-derived prolactin has been shown not only to induce IL-6 and IL-23 production by DCs, the former of which serve a critical role in altering the phenotypes of Tregs, but also to alter Treg properties, leading to intestinal inflammation (75). Chronic restraint stress has been shown to result in a marked decrease in CD4 T cell numbers and intracellular IFN-γ expression, while increasing IL-4 production. It was also found that, in chronically stressed mice, treatment with 4-methylhistamine (4-MeH) agonist was able to restore the immune response, particularly via the production of Th1 cytokines. Stimulation of the histamine 4 receptor with 4-MeH modulates the effects of chronic stress on the Th1/Th2 cytokine balance (111). The sympathetic and neuroendocrine responses to psychosocial stress have been shown to have a significant impact on cancer, partly through the regulation of inflammatory mediators (112). Psychological stress increases extracellular adenosine triphosphate (ATP), IL-1β and TNF-α in the hippocampus, and activates the inflammasomes via the release of ATP and the stimulation of the purinergic type 2X7 receptor (16). Inflammasomes are multiprotein complexes that operate as platforms for the activation of caspase-1 and can be categorized based on their main constituent as either NLR family pyrin domain containing 1 (NLRP1), NLRP3, NLR family CARD domain containing 4, NLRP6 or absent in melanoma 2. The activation of inflammasomes can lead to the conversion of inactive inflammation mediators to active ones (IL-1β and IL-18), and, subsequently, the active inflammation mediators are secreted to the cell exterior to modulate cell function in an autocrine or paracrine manner. This process may mechanistically explain the link between inflammasome activation and tumorigenesis, angiogenesis or metastasis (113,114). Furthermore, the external IL-1β can initiate self-reinforcing feedback loops to further perpetuate its existence through the IL-1R-MyD88-NF-κB pathway by inflammasome activators (115). Based on the aforementioned findings, the inhibition of inflammasomes or neutralization of their products can have profound effects on carcinogenesis and tumor progression. The stress hormones NE and Epi can enhance IL-8 expression and thereby mediate the effects of stress on the growth and metastasis of ovarian cancer (116). IL-8 gene silencing with liposomal small interfering RNA incorporated in 1,2-dioleoyl-sn-glycero-3-phosphocholine has been shown to decrease tumor growth and angiogenesis in ovarian cancer. In addition, the increase of pro-inflammatory cytokines has been associated with irritability, insomnia and fatigue, which, in turn, are associated with cancer (117) (Fig. 3).

Effects of stress on chemo-resistance (multidrug resistance). At present, chemotherapy is one of the main treatment strategies for malignant tumors. However, a number of chemotherapeutic approaches fail due to intrinsic or acquired drug resistance, particularly multidrug resistance. Multiple studies have focused on the mechanisms underlying multidrug resistance in cancer, including DNA damage repair (118) and abnormalities in the expression and function of transporters of the ATP-binding cassette superfamily. P-glycoprotein is the member of this mechanism that has been most frequently reported in association with tumor drug resistance, cancer stem cell, epithelial-mesenchymal transitions and hypoxia (119,120). A study on mice showed that psychological stress reduced the antitumor effects of chemotherapeutic drugs and induced chemo-resistance in breast cancer by upregulating multidrug resistance protein 1 via adrenergic stimulation (121). Stress hormones induced by restraint stress, including cortisol and epinephrine, can decrease the efficacy of paclitaxel in triple-negative breast cancer through the induction of DNA damage and ATR serine/threonine kinase and p21 expression (122). Adrenaline can induce chemo-resistance in HT-29 colon adenocarcinoma cells by upregulating the ATP binding cassette subfamily B member 1 gene expression via α2-adrenergic receptors (123), as well as cisplatin resistance through the activation of the NF-κB pathway and subsequent induction of miR-155 (124). One study showed that miR-155 is responsible for the drug resistance in breast cancer cells, by targeting fork-head box O3 (125). Meanwhile, injections of epinephrine or immobilization stress can counteract the antitumor effects of phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitors on prostate cancer xenografts in mice (126). A dynamic network model of apoptosis regulation in prostate cancer indicated that psychological stress could trigger a synergism pattern switch in drug combination therapy (127). However, it is important to note that chemotherapy itself may generate or deteriorate psychological stress, which is known to be accompanied by chronic elevation of plasma catecholamine, conversely leading to chemo-resistance (121). Psychological stress has been found to attenuate the anti-angiogenic efficacy of sunitinib through the activation of β-adrenergic signaling and the promotion of tumor angiogenesis, which, however, can be improved by the use of β-blockers (39). Stress hormones have also been shown to promote resistance to epidermal growth factor receptor (EGFR) inhibitor in non-small cell lung cancer, which can be abrogated by combinations of β-blockers and EGFR tyrosine kinase inhibitors (53). Furthermore, certain gut microbiota, such as *Escherichia coli* strains, can decrease the efficacy of chemotherapeutic agent gemcitabine by metabolizing and deactivating the active form of the drug (128).

4. Conclusion

Stress is one of the fundamental survival mechanisms in nature; it begins with a stressor, leading to stress perception and subsequently resulting in a stress response. Stress can be divided into acute and chronic, mainly according to its respective salubrious or detrimental effects on the health of an individual. Several studies have demonstrated that stress, particularly chronic stress, serves an important role in tumorigenesis and metastasis. Relevant and effective animal models are essential for the study of the effects of stress on cancer and the underlying mechanisms. The induction of CMS or chronic restraint stress has been widely used for the development of experimental models. The stress-induced persistent activation of the HPA axis and SNS has been shown to result in a cascade reaction leading to cross-talk among the neuroendocrine system, the immune system, gut microbiota and inflammation. Further elucidation of the influence of the interactions among these factors in mediating stress-associated effects on tumorigenesis and metastasis is imperative. Novel approaches
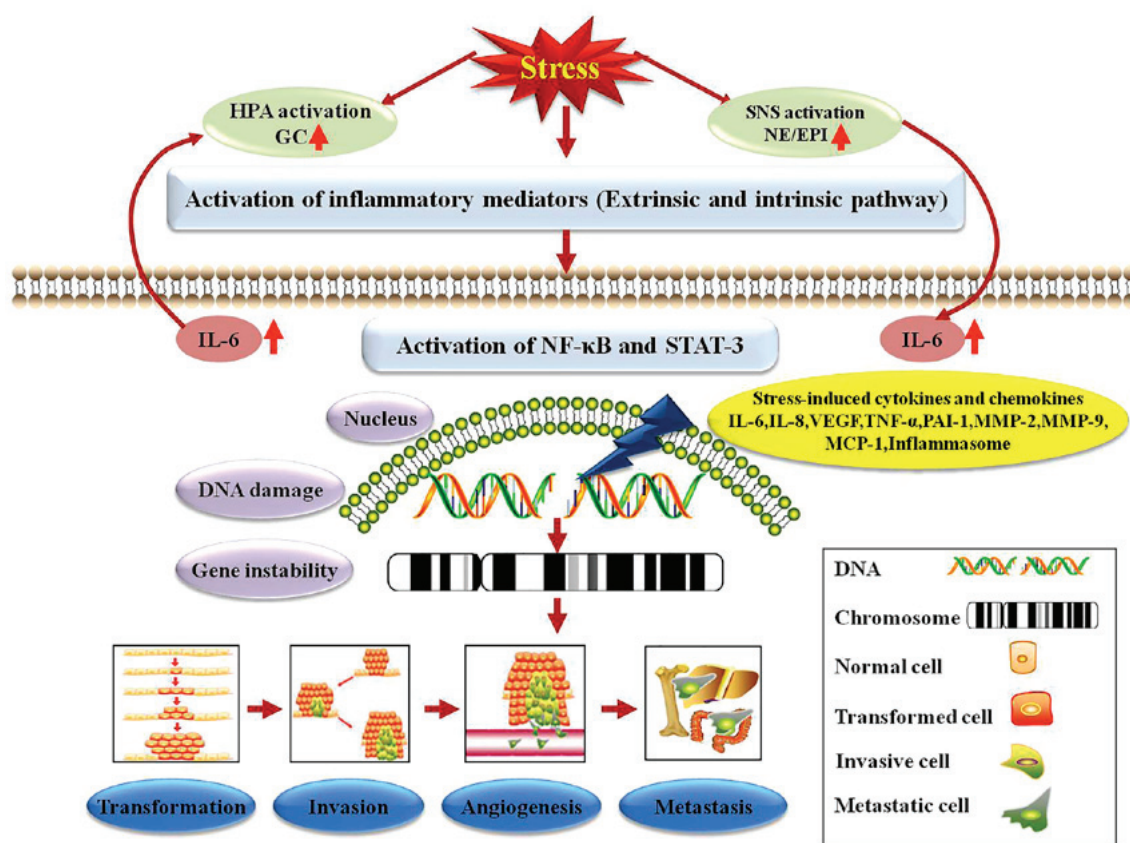
Figure 3. Effects of stress-induced inflammation on tumorigenesis, invasion, angiogenesis and metastasis. Stress, particularly chronic stress, can not only lead to the activation of the HPA axis and SNS, but also activate inflammatory mediators in extrinsic and intrinsic pathways. The transcription factors NF-κB and STAT3 are the two major pathways linking cancer to inflammation, which can be activated by the majority of cancer risk factors, including stress, diet, infectious agents and environmental pollutants. Stress-induced cytokines and chemokines, including IL-8, IL-8, VEGF, MMP-2 and inflammasomes, have a damaging effect on DNA and can result in gene instability and mutations closely associated with cell transformation, invasion, angiogenesis and metastasis. Furthermore, there exists a vicious circle between the activation of the SNS and the HPA axis, and the secretion of IL-6. Specifically, the activation of SNS can increase the release of IL-6, while IL-6 can trigger the activation of the HPA axis and promote the release of CRH, ACTH and cortisol. HPA, hypothalamic-pituitary-adrenal; SNS, sympathetic nervous system; NF-κB, nuclear factor-κB; STAT3, signal transducer and activator of transcription 3; IL, interleukin; VEGF, vascular endothelial growth factor; MMP, metalloproteinase; CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotropic hormone; NE, norepinephrine; Epi, epinephrine; GC, glucocorticoid; IL, interleukin; TNF-α, tumor necrosis factor-α; MMP, matrix metalloproteinase; MCP-1, monocyte chemoattractant protein-1.

to the prevention and blockage of the harmful effects of stress on tumorigenesis and metastasis are required.

5. Practical perspectives

Stress and stress-associated disorders have become prevalent in modern societies due to the fast-paced nature of contemporary lifestyles. Due to their prevalence, such disorders are often concealed, which has detrimental effects to health. Studies have demonstrated that exposure to stress during critical periods in human development is sufficient for it to have severe, long-term consequences (35,129). In addition, chronic stress may lead to epigenetic heritable modifications, suggesting a possible propagation across generations (55). It is noteworthy that stress may exist universally during the diagnosis and subsequent treatment process in patients with cancer (130). On a positive note, it has been shown that effective intervention in cancer patients presenting with stress can improve their immune function and physical activity, and social support can modulate cancer-related pathways and improve the levels of certain biomarkers associated with a better prognosis and longer survival (131). Studies have also

revealed that disturbances in mood, anxiety and irritability may precede the appearance of a medical disorder, and that stress-prone personalities or unfavorable coping mechanisms and negative emotional responses are associated with a higher incidence, poorer survival and higher mortality rates in patients with cancer (132). Dhabhar (11) proposed the stress spectrum model and concept, so as to reconcile the potentially beneficial effect of stress with the harmful; according to the stress spectrum model, one can keep fit by minimizing chronic stress, maximizing the resting zone of low/no stress and optimizing the acute stress response.

In the research findings discussed within the present review, it was demonstrated that effective stress prevention and management are plausible and imperative, and that the primary, secondary and tertiary prevention strategies should receive adequate recognition. In particular, moderate exercise, a healthy diet, high-quality sleep and emotional management are key aspects that can be improved in the lives of patients with stress-induced cancer, so that they benefit from them. Regular exercise can assist in keeping the short-term stress response well-oiled, finely-tuned and ready for fight-or-flight (11), as well as improving the physical and emotional well-being of

an individual. Furthermore, regular exercise has also been shown to reduce the risk for breast cancer recurrence (133). The type, intensity, duration and frequency of exercise should be tailored to the constitution an individual. A number of traditional methods of exercise, including five-animal boxing, eight-section brocade, changing tendon exercise, meditation and yoga, may contribute to successful stress management.

The present review found that diet and gut microbiota play an important role in tumorigenesis and metastasis. Therefore, closer attention should be paid to dietary strategies, and particularly the maintenance of healthy-eating habits. Furthermore, developing effective microbial agents is necessary and promising with regard to the reduction of cancer risks. An association has been identified between lack of sleep or sleep disturbances such as insomnia, fatigue, obstructive sleep apnea and restless legs syndrome, and depression or anxiety (134). The latter are also common among cancer patients, and often comprise the symptoms that lead to the diagnosis of certain types of cancer (135). In addition, circadian cortisol rhythm disruptions serve as an important indicator and/or mediator of the deleterious effects of chronic stress (1). In view of this, future studies are warranted to better understand the mechanisms underlying the effects of stress on tumorigenesis and metastasis.

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QL and YW put forward the conception and design of the manuscript, and ZZZ and YW were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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