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Review Article

Decoding the metastatic nexus: how chronic stress reprograms neuroendocrine-metabolic-microbiome circuits to fuel tumor metastasis

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Abstract: Metastasis, the leading cause of death in patients with solid tumors, involves the spread of cancer cells to distant organs. While genetic and environmental factors contribute, chronic stress is a crucial factor in metastatic progression by disrupting neuroendocrine, immune, metabolic, and microbial homeostasis. This review synthesizes evidence linking chronic stress to tumor metastasis through three pathways: (1) direct effects on tumor cell metabolism, (2) remodeling of the tumor microenvironment, and (3) dysregulation of the gut microbiota. Describe how activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system influence epithelial-mesenchymal transition, immune evasion, and angiogenesis via β-adrenergic and glucocorticoid receptor signaling. Explore how microbial metabolites and barrier dysfunction influence immune and neuroendocrine circuits, creating a pro-metastatic loop. Finally, we highlight therapeutic strategies, including psychological interventions and pharmacologic approaches, to alleviate chronic stress. This review proposes a mechanistic framework linking neuroendocrine signaling, metabolic reprogramming, and the microbiome-immune axis.

Keywords: Chronic stress, tumor metastasis, neuroendocrine regulation, tumor microenvironment, gut microbiota, metabolic reprogramming

Introduction

Tumors, as one of the most significant factors affecting human health, have become a focal point of global medical research. This is especially true for patients with metastatic solid tumors, whose five-year survival rate ranges from 5% to 30%, highlighting the complexity of the metastatic process and the challenges of treatment. Unfortunately, approximately 90% of patients with cancer ultimately die from tumor metastasis [1, 2] underscoring the importance of controlling metastasis, which is key to improving patients with cancer survival rates. Controlling tumor metastasis is crucial for enhancing survival outcomes. Tumor metastasis involves not only the spread of cancer cells to other parts of the body but also severe damage to normal tissue and organ function, accompanied by a series of complications. For instance, bone metastasis can lead to fractures and severe pain, significantly impacting the patient's quality of life [3]; Lung metastasis, on the other hand, may cause symptoms such as difficulty breathing and hemoptysis [4], presenting a substantial threat to patient safety. Additionally, liver metastasis can severely affect the liver's metabolism and detoxification functions, potentially resulting in life-threatening conditions such as liver failure [5]. According to statistics, approximately 18 million people are diagnosed with cancer each year, with 10-15% experiencing metastasis, highlighting the widespread and severe nature of this issue. Unfortunately, existing treatment options still fail to effectively address the challenge of tumor metastasis, making further research and breakthroughs in the medical community urgently needed.

Chronic stress plays a critical role in the complex process of tumor metastasis. Numerous

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studies have demonstrated that prolonged exposure to chronic stress can significantly suppress immune system function, reducing the body's ability to detect and eliminate tumor cells. This suppression may also promote immune evasion by tumor cells, exacerbating disease progression and potentially leading to treatment resistance [6, 7]. Therefore, in-depth research into the specific mechanisms by which chronic stress facilitates tumor metastasis is of immense importance for uncovering the underlying processes of metastasis and developing new, more effective treatment strategies.

Purpose and significance

This review systematically examines the three main pathways through which chronic stress promotes tumor metastasis via the "neural-tumor microenvironment-microbial community" interaction network. It provides an in-depth analysis of the mechanistic basis for the complex interactions between multiple organs, such as the brain-gut-tumor axis. Additionally, this study identifies crucial intervention targets for drug development aimed at effectively responding to and regulating stress-related pathways. Although studies have established a clear connection between chronic stress and tumor metastasis, the specific molecular mechanisms remain underexplored and require further investigation. This review integrates various system-level mechanisms, addressing the gap in mechanistic connectivity and offering robust theoretical support for the prevention and control of tumor metastasis, thus advancing research in related fields.

Chronic stress

Definition

Stress, a complex and pervasive phenomenon, is a non-specific systemic response that occurs when internal and external environmental stimuli exceed the body's tolerance threshold [8]. This reaction is not merely a simple response to external challenges but involves a series of intricate physiological mechanisms. The most central of these mechanisms are the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Activation of these systems leads to abnormal hormone release, which in turn triggers gene signaling pathways related to tumor development, promoting biological processes associated with cancer [9, 10]. The complexity and significance of this mechanism underscore the close relationship between stress and health, particularly in the onset and progression of cancer.

Chronic stress is a prolonged physiological state resulting from sustained exposure to various internal or external stimuli. The hallmark of this state is the persistent dysfunction of the HPA axis and SNS [9], which not only disrupts normal body functions but can also precipitate a range of health issues. Long-term stress responses contribute to hippocampal neuronal damage and abnormal changes in prefrontal cortex synapses through complex biochemical signaling pathways, particularly involving glucocorticoids and catecholamines [11]. Additionally, chronic physiological stress exacerbates the deposition of amyloid beta protein and compromises the gastrointestinal barrier function, leading to worsened organ complications such as neurodegenerative diseases, gastrointestinal dysfunction, and mental health disorders [12, 13]. These outcomes significantly impact overall health and quality of life.

Classification

Chronic stress can be categorized into four types based on the triggering factors: psychological, physiological, social, and comprehensive stress. Chronic psychological stress primarily stems from long-term psychological pressure, manifesting as anxiety, depression, tension, and mental fatigue. Patients with cancer are particularly affected by psychological stress. For example, patients with cancer experience sustained psychological pressure after diagnosis, which can disrupt hormonal balance and exacerbate cancer cell proliferation and metastasis through hormone-mediated signaling pathways [14]. Physiological chronic stress is triggered by continuous physiological stimuli, typically arising from chronic pain and organ dysfunction associated with long-term diseases [15]. Chronic social stress refers to the sustained psychological and physiological tension resulting from prolonged exposure to social relationships or environmental stressors. Social stress can lead to excessive cortisol secretion, which in turn causes metabolic imbalances [10, 16]. Comprehensive chronic stress refers to the combined effect of multiple factors, such as psychological, physiological, and social stressors, often experienced simul-

taneously by patients with cancer, leading to cumulative effects that accelerate the progression of the disease [10].

Reaction mechanism

The physiological mechanism underlying chronic stress has become well-defined, primarily reflecting the complex interaction between the HPA axis and the SNS, along with the cascade reactions they trigger. When an individual perceives stress, neurons in the hypothalamus rapidly release corticotropin-releasing factor (CRF), which acts as a signal to activate the anterior pituitary gland, stimulating its secretion of adrenocorticotropic hormone (ACTH) through the pituitary portal system [17]. ACTH then serves as a key trigger, stimulating the adrenal cortex to release glucocorticoids such as cortisol. However, sustained elevation of cortisol levels leads to failure of the HPA axis negative feedback mechanism, resulting in a gradual reduction in glucocorticoid receptors (GR) sensitivity. This, in turn, weakens the central negative feedback inhibition signal, creating a vicious cycle of "stress hormone elevation feedback failure". Prolonged persistence of this cycle ultimately causes irreversible damage to hippocampal neurons [18]. Meanwhile, cortisol also weakens the body's anti-inflammatory response by inhibiting immune cell function and promoting the release of pro-inflammatory mediators such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) [10]. These inflammatory mediators can cross the blood-brain barrier, activate central inflammation, and initiate a positive feedback loop of "HPA axis-activated inflammatory response" [18]. In summary, chronic stress severely disrupts physiological rhythms by persistently activating the HPA axis and SNS, acting as a core driving mechanism behind various pathological processes such as depression, neurodegenerative diseases, and immune system disorders. This pathological network involves a range of changes, including damage to neural plasticity and immune system imbalance, presenting a complex and severe health challenge (**Figure 1**).

Tumor metastasis

Definition

Tumor metastasis is a complex and critical biological process in which tumor cells spread from their primary site to surrounding tissues and distant organs. This process serves as both a key indicator of tumor development and progression and a significant factor influencing patient prognosis and treatment strategies. As early as 1889, the renowned pathologist Stephen Paget proposed a forward-thinking theory, suggesting that tumor metastasis depends on the interaction between specific types of cancer cells (referred to as "seeds") and the microenvironment of specific organs (known as "soil") [19]. This theory continues to provide valuable insight into the understanding of tumor metastasis. Current research indicates that the metastatic potential of tumor cells is not only linked to their inherent characteristics but is also closely tied to the complex interactions between stable environmental factors that promote tumor cell growth, survival, angiogenesis, invasion, and metastasis [20]. Tumor cells first detach from the primary tumor and subsequently invade vascular systems, such as capillaries and lymphatic vessels. Once within these blood vessels, the cells are able to survive and gradually infiltrate secondary sites, where they establish a microenvironment that supports the necessary nutrients and blood supply for their growth. This series of processes not only highlights the adaptability of tumor cells but also identifies potential therapeutic targets for addressing tumor metastasis.

Transfer mechanism

Phenotypic changes promote metastasis

Epithelial-mesenchymal transition (EMT) is a critical step in tumor metastasis, playing a pivotal role in the metastatic process. In the complex tumor microenvironment, transforming growth factor beta (TGF-β) upregulates the expression of key transcription factors, such as Snail, Twist, and ZEB1, by activating the Smad2/3 signaling pathway. This cascade of molecular changes leads to significant alterations in the expression of E-cadherin [21], ultimately disrupting intercellular connections and breaking the tight junctions between cells. Concurrently, the expression levels of N-cadherin and vimentin are significantly increased, which not only enhances cell motility but also facilitates the effective detachment of tumor cells from the primary tumor site [22], further advancing metastasis (**Figure 2**, inside the left box and pointing to the EMT process).

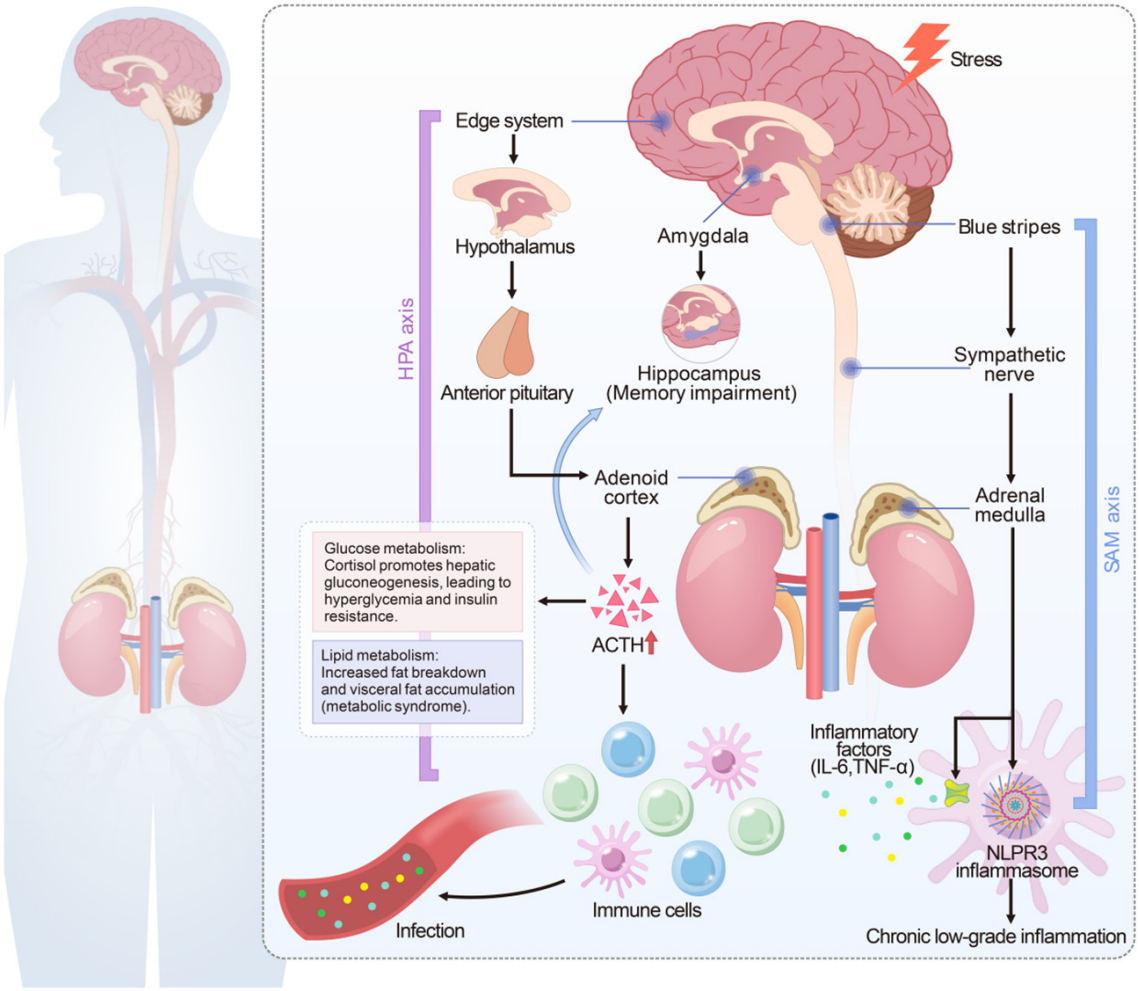

Figure 1. Mechanism of the chronic stress response. Chronic stress activates the HPA axis and the SNS, resulting in alterations in neuroendocrine and immune function, metabolic dysregulation, and disruption of physiological homeostasis. *The figure was created using Adobe Illustrator*. *Abbreviations*: HPA axis, hypothalamic-pituitary-adrenal axis; SNS, sympathetic nervous system; ACTH, adrenocorticotropic hormone; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; IL-6, interleukin-6; TNFα, tumor necrosis factor alpha.

Additionally, tumor cells can secrete urokinase-type plasminogen activator, which activates plasminogen and, in conjunction with matrix metalloproteinases, degrades the basement membrane, enabling tumor cells to invade the surrounding extracellular matrix [23] (**Figure 2**, MMP9 related processes within tumor cells on the right). Subsequently, tumor cells reactivate their protein hydrolysis systems, penetrate the vascular wall, regulate the microenvironment, and recruit host cells, ultimately establishing a neovascularization network. These processes work in concert, culminating in the formation of metastatic tumors [24] (**Figure 2**, Hypoxia, reactive oxygen species [ROS], and gut microbiota metabolites (LPS, SCFAs, DCA) drive the activation of HIF-1α, NF-κB, and Wnt/β-catenin signaling pathways, thereby inducing EMT, angiogenesis, and immune suppression. Red arrows indicate tumor-promoting signals, whereas blue blunt-ended lines denote inhibitory signals. Distinct cell types are labeled with different colors. As detailed in this section, the TGF-β/Smad pathway is a central regulator of EMT; notably, this process may also be activated by chronic stress-mediated signaling, as discussed in Sections 4.1 and 5.2.5.2.

Gut microbiota promotes tumor cell metastasis

The gut microbiota, a complex and diverse microbial ecosystem, plays a crucial role in tumor progression. Its various metabolites, such as lipopolysaccharides (LPS), bile acids

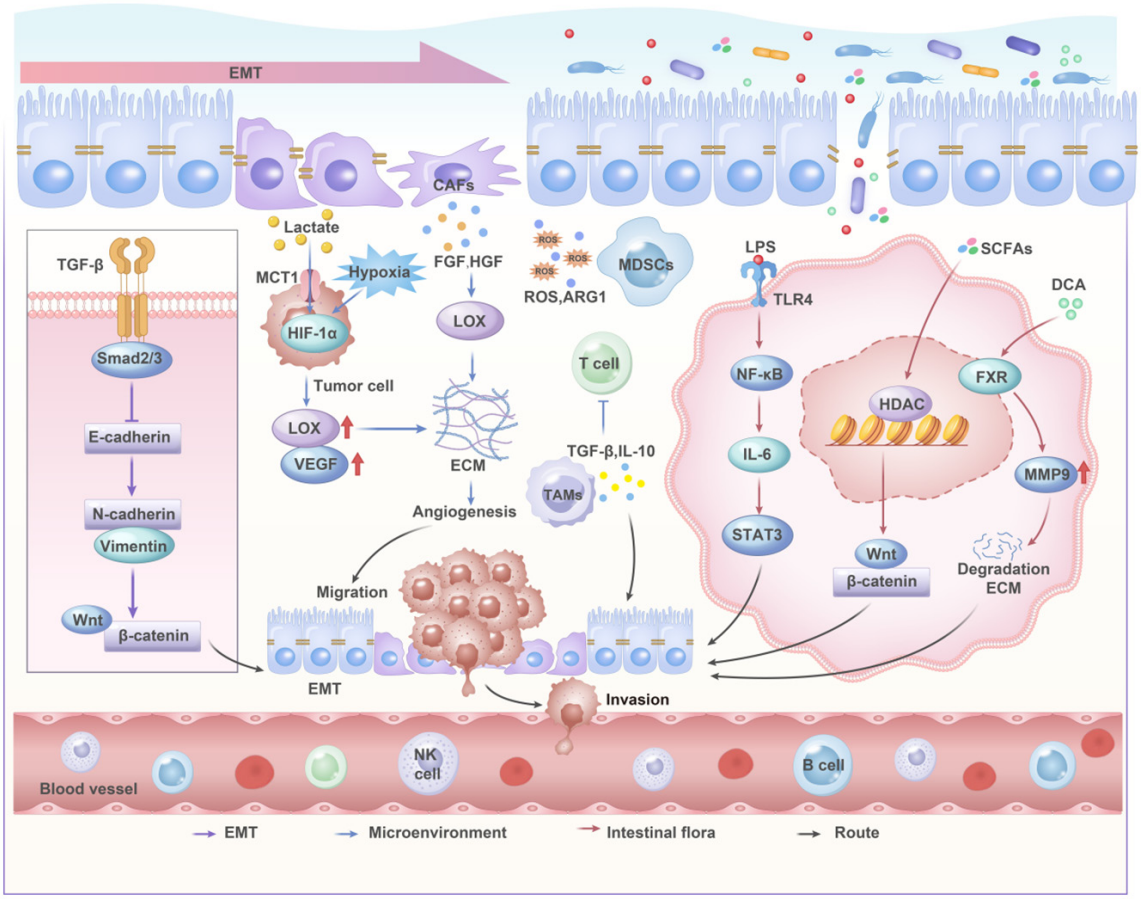

Figure 2. Mechanisms of tumor metastasis under chronic stress. Chronic stress promotes tumor metastasis by inducing EMT, remodeling the tumor microenvironment, and altering the gut microbiota. In the tumor microenvironment (TME), hypoxia and reactive oxygen species (ROS) induce stable expression of HIF-1α in tumor cells, which subsequently transcribes and activates VEGF, stimulating endothelial cells to form new blood vessels (angiogenesis) while upregulating matrix-degrading enzymes such as LOX and MMP9, thereby remodeling the extracellular matrix (ECM). Concurrently, cytokines such as TGF-β, IL-6, IL-10, secreted or acting in a paracrine manner, activate the Smad2/3, STAT3, and NF-κB pathways. The TGF-β/Smad axis, on the one hand, drives epithelial-mesenchymal transition (EMT) by inhibiting E-cadherin, inducing N-cadherin, Vimentin, and β-catenin nuclear translocation, endowing tumor cells with enhanced migratory and invasive capabilities; on the other hand, it recruits and polarizes tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), which express high levels of ROS, arginase-1 (ARG1), and IL-10, further inhibiting the killing function of T, NK, and B cells. Gut microbiota-derived short-chain fatty acids (SCFAs) and deoxycholic acid (DCA) modulate immune balance by activating FXR and inhibiting HDAC, respectively, while bacterial lipopolysaccharide (LPS) amplifies the NF-κB mediated inflammatory pathway through TLR4 signaling. Additionally, lactic acid travels between tumor cells and immune cells via monocarboxylate transporter-1 (MCT1), maintaining an acidic microenvironment and enhancing immune suppression. Therefore, the three major signaling networks of hypoxia ROS HIF-1α-VEGF EMT, TGF-β/Smad-STAT3-NF-κB, and Wnt/β-catenin are interwoven, jointly promoting tumor angiogenesis, matrix degradation, immune escape, and distant metastasis, forming a complete ecosystem for malignant progression. *The figure was created using Adobe Illustrator. Abbreviations*: EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor beta; MCT1, monocarboxylate transporter 1; HIF-1α, hypoxia-inducible factor-1 alpha; LOX, lysyl oxidase; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; ECM, extracellular matrix; ROS, reactive oxygen species; ARG1, arginase 1; IL-10, interleukin 10; TAMs, tumor-associated macrophages; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; IL-6, interleukin 6; STAT3, signal transducer and activator of transcription 3; HDAC, histone deacetylase; FXR, farnesoid X receptor; MMP9, matrix metallopeptidase 9; DCA, deoxycholic acid.

(BA), and short-chain fatty acids (SCFAs), not only significantly impact host health but also reshape the tumor microenvironment (TME) and activate key signaling pathways, greatly affecting the invasiveness and metastatic potential of tumor cells. For instance, lipopoly-

saccharides (LPS) activate the NF-κB signaling pathway by binding to TLR4, which induces immune cells to secrete cytokines that promote metastasis (**Figure 2**, LPS related processes within tumor cells on the right). This process reduces the adhesion between tumor cells and significantly enhances their migratory capacity [25, 26]. Additionally, the secondary bile acid deoxycholic acid (DCA) activates FXR receptors, upregulates MMP9 and IL-8, and promotes angiogenesis by degrading the basement membrane, further facilitating tumor growth and spread [27] (**Figure 2**, DCA related processes within tumor cells on the right). Propionate, on the other hand, activates the GPR43 receptor, initiating the PI3K/AKT signaling pathway, which enhances cell survival and migration [28]. These complex interactions and signaling mechanisms together constitute the intricate relationship between the gut microbiota and tumor cells, highlighting the potential role and importance of the microbiota in tumor development.

Microenvironmental changes promote tumor metastasis

The tumor microenvironment (TME) is a complex ecosystem that tumor cells rely on for survival and reproduction. It includes various critical components, such as immune cells, stromal cells, extracellular matrix (ECM), and numerous signaling molecules, all of which coordinate and interact delicately to promote tumor metastasis [29]. Stromal cells can effectively activate EMT by secreting cytokines like interleukin-6 (IL-6) and transforming growth factor-β (TGF-β). Additionally, stromal cells transmit pro-metastatic proteins through exosomes, reshaping the extracellular matrix structure. This remodeling not only provides physical support and channels for tumor cell invasion but also creates favorable conditions for metastasis [30]. During the dynamic process of metastasis, pro-inflammatory neutrophils are gradually replaced by immune-suppressive cells, particularly M2 macrophages. This polarization from M1 to M2 macrophages provides a crucial biological basis and pathway for tumor cells to evade immune surveillance [31]. Moreover, chemokines in the microenvironment exhibit dual effects. Some chemokines recruit CD4+/CD8+ T cells and natural killer (NK) cells, exerting a positive anti-metastatic effect, while others recruit immune cells that promote tumor growth, thereby facilitating tumor immune escape [32, 33].

Evidence that chronic stress promotes tumor metastasis

Chronic stress promotes tumor metastasis through multiple interconnected biological mechanisms organized within a “neuro-microenvironment-microbiome” triadic network. The following sections outline the key evidence, beginning with neuroendocrine activation as the primary initiator that triggers a cascade leading to immune dysregulation within the tumor microenvironment (Section 5.2) and disruption of the gut microbiota homeostasis (Section 5.3). The relevant evidence is summarized as follows:

Activation of the neuroendocrine system and receptor signaling pathways

As detailed in Section 2.3, chronic stress potently activates the HPA axis and the SNS, resulting in the aberrant release of glucocorticoids and catecholamines (such as norepinephrine and epinephrine). In the context of cancer, these neuroendocrine factors activate specific receptor-mediated signaling pathways that profoundly influence tumor progression. Catecholamines promote tumorigenesis primarily by binding to and activating β-AR. This interaction upregulates key pro-tumorigenic factors such as VEGF and IL-6, thereby accelerating angiogenesis and facilitating tumor cell growth, EMT, and metastasis [34, 35]. The molecular details of EMT, involving transcription factors such as Snail, Twist, and E-cadherin downstream of various triggers, are described in Section 3.2.1. The IL-6/JAK/STAT3 signaling axis, once activated, serves as a central hub driving multiple pro-metastatic processes, including inflammatory responses, metabolic reprogramming, and immune suppression, as discussed in subsequent sections (Sections 5.1.1.3 and 5.2.5.2). Similarly, VEGF is a key mediator of stress-induced angiogenesis (see Section 5.2.5.3). Furthermore, chronic stress enhances cancer cell invasion and migration through alternative neurotransmitter pathways, such as the acetylcholine (ACh)/α5-nicotinic acetylcholine receptor (α5-nAChR)/FHIT axis [36]. Given its pivotal role, targeting the β-AR pathway has emerged as a promising therapeutic strategy to mitigate stress-induced tumor

metastasis. For instance, the natural compound baicalin has been shown to reduce chronic stress-induced tumor metastasis by directly targeting β-AR [37].

In summary, neuroendocrine activation forms the cornerstone of the triadic network, directly priming both tumor cells and the surrounding microenvironment for metastasis and, as discussed later, indirectly perturbing the distal gut ecosystem.

Immunosuppression and microenvironment remodeling

Chronic stress reshapes the tumor microenvironment by affecting specific immune cell functions, altering the release of inflammatory cytokines, and generating ROS. Chronic stress induces the formation of neutrophil extracellular traps (NETs), which inhibit T cell activity and promote cancer lung metastasis [38]. It also disrupts the polarization balance of tumor-associated macrophages (TAMs), thereby promoting the growth of hepatocellular carcinoma [39]. Furthermore, chronic stress reshapes the lymphatic vascular system and activates the IL-6/STAT3 pathway, promoting EMT and tumor cell proliferation, migration, and invasion [40, 41]. Activation of Kupffer macrophages and the induction of ROS production further contribute to the progression of hepatocellular carcinoma [42, 43].

Metabolic reprogramming

Studies have shown that chronic stress can reprogram fatty acid metabolism through the CXCL3-mediated Wnt/β-catenin pathway, promoting the proliferation and metastasis of oral squamous cell carcinoma (OSCC) [44]. Additionally, under chronic stress conditions, the arachidonic acid metabolite prostaglandin E2 (PGE2) regulates stress responses, immune functions, and inflammatory pathways [45]. Chronic stress also induces PGC1α, which interacts with specific transcription factors to influence mitochondrial respiration, the ROS defense system, and fatty acid metabolism, promoting cancer cell survival and metastasis in harsh microenvironments [46]. Moreover, chronic stress upregulates peroxisome proliferator-activated receptor alpha (PPARα), regulating fatty acid oxidation and thereby promoting cell survival.

The metabolic rewiring described here functionally links neuroendocrine signals to the tumor microenvironment. Metabolites such as lactate and fatty acids act as soluble mediators that contribute to the acidification, bioenergetic corruption, and immune suppression characteristic within the stressed TME, thereby closing the loop between the “neuro” and “microenvironment” components of the network.

Three mechanisms by which chronic stress promotes tumor metastasis

Direct effects of chronic stress on tumor cells

Chronic stress is a central mechanism that reprograms tumor metabolism through activation of the SNS and its downstream signaling cascades. The resulting release of catecholamines, such as norepinephrine, binds to and activates β-AR on tumor cells. This interaction triggers the intracellular cAMP/PKA signaling pathway, a main regulatory axis that phosphorylates multiple downstream targets to coordinate diverse biological processes, as detailed in the following sections.

Chronic stress affects the glucose metabolism of tumor cells

Chronic stress directly promotes the molecular mechanisms of tumor metastasis by altering the glucose metabolism of tumor cells. This section summarizes three key directions based on cutting-edge research progress:

Chronic stress enhances glycolysis through the HPA/SNS axis: Chronic stress significantly increases the levels of aerobic glycolysis products and enzymes in tumor tissue. The β-AR/cAMP/PKA axis, as a key mediator, promotes glycolysis through multiple specific effectors [47]. For instance, it upregulates GLUT1/GLUT3 (glucose transporters) and key glycolytic enzymes such as hexokinase 2 (HK2), lactate dehydrogenase A (LDHA), and phosphofructokinase platelet type (PFKP) via the downstream transcription factor CREB1, thereby promoting glucose uptake and lactate production [48] (**Figure 3**, β-AR/CREB1 pathway). Additionally, stress-induced GLUT1 acts synergistically with hypoxia-inducible factor HIF-1α to further enhance glycolysis and accelerate malignant progression [49]. Furthermore, PKA directly phosphorylates and activates PFKFB3, a criti-

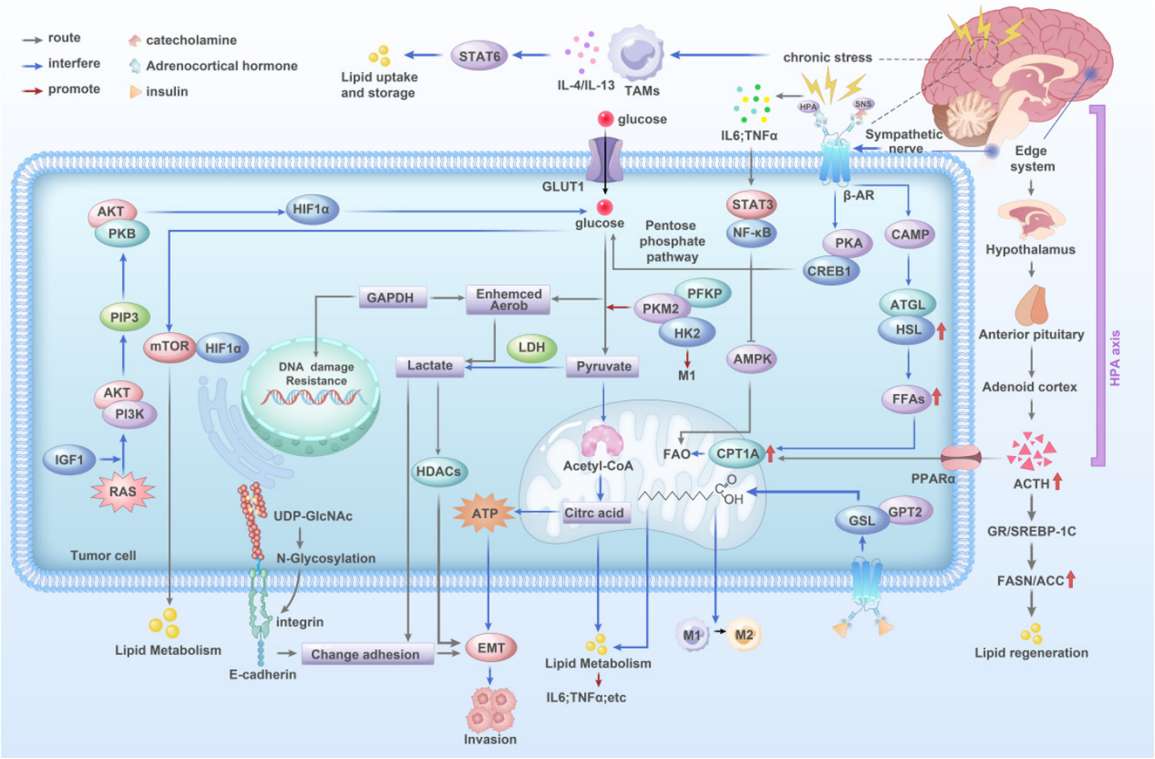

Figure 3. Chronic stress disrupts glucose and lipid metabolism in tumor cells. Chronic stress reprograms tumor cell metabolism by enhancing glycolysis, promoting lipolysis, and altering energy pathways via neuroendocrine and inflammatory signaling. Chronic stress, as a key driving factor for tumor progression, reprograms the energy metabolism of tumor cells through a series of complex signaling and metabolic pathways. Firstly, chronic stress activates the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), releasing adrenal cortex hormones and catecholamines. These hormones activate protein kinase A (PKA) through β-adrenergic receptors (β-AR), thereby promoting the phosphorylation of cAMP response element-binding protein 1 (CREB1) and enhancing the metabolic activity of tumor cells. Secondly, chronic stress enhances the glycolysis process of tumor cells, increasing glucose uptake through glucose transporter 1 (GLUT1) and converting glucose to pyruvate through key glycolytic enzymes such as phosphofructokinase (PFKP) and pyruvate kinase M2 (PKM2). Subsequently, lactate dehydrogenase (LDH) converts pyruvate to lactate, providing a rapid energy source for tumor cells. Meanwhile, chronic stress promotes fat breakdown, activating hormone-sensitive lipase (HSL) and triglyceride lipase (ATGL) to break down fat into free fatty acids (FFAs). These FFAs enter mitochondria through carnitine palmitoyltransferase 1A (CPT1A), participate in β-oxidation, produce acetyl-CoA, and further enter the tricarboxylic acid cycle (TCA cycle) to generate energy. Additionally, chronic stress activates the signal transduction and transcription activation factor 3 (STAT3) and nuclear factor kappa B (NF-κB) signaling pathways through inflammatory factors such as IL-6 and TNFα, as well as promotes phosphorylation of CREB1 through activation of β-AR and PKA, further affecting the metabolic gene expression of tumor cells. Finally, chronic stress not only enhances the energy production of tumor cells, but also promotes epithelial-mesenchymal transition (EMT) by activating hypoxia-inducible factor 1 alpha (HIF1 alpha) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), enabling tumor cells to acquire invasion and metastasis capabilities, while enhancing DNA damage resistance, enabling tumor cells to better adapt to the stress environment and promote their survival and spread. The interaction between these signaling pathways and metabolic pathways forms a complex network that collectively drives tumor progression. *The figure was created using Adobe Illustrator.* *Abbreviations*: HPA axis, hypothalamic-pituitary-adrenal axis; ACTH, adrenocorticotropic hormone; IL-6, interleukin 6; TNFα, tumor necrosis factor alpha; IL-4, interleukin 4; STAT6, signal transducer and activator of transcription 6; IL-1β, interleukin-1 beta; TAMs, tumor-associated macrophages; SREBP-1c, sterol regulatory element-binding protein 1c; FASN, fatty acid synthase; ACC, acetyl-CoA carboxylase; GLUT1, glucose transporter 1; HIF-1α, hypoxia-inducible factor 1 alpha; PKB, protein kinase B; PIP3, phosphatidylinositol(3,4,5)-trisphosphate; PI3K, phosphoinositide 3-kinase; IGF1, insulin-like growth factor 1; RAS, rat sarcoma virus oncogene; mTOR, mechanistic target of rapamycin; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; LDH, lactate dehydrogenase; UDP-GlcNAc, uridine diphosphate N-acetylglucosamine; ATP, adenosine triphosphate; EMT, epithelial-mesenchymal transition; PKM2, pyruvate kinase M2; PFKP, phosphofructokinase; HK2, hexokinase 2; M1/M2, macrophage polarization states; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor kappa B; AMPK, AMP-activated protein kinase; FAO, fatty acid β-oxidation; CPT1A, carnitine palmitoyltransferase 1A; β-AR, beta-adrenergic receptor; CREB1, cAMP responsive element-binding protein 1; CAMP, cyclic adenosine monophosphate; ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase; FFAs, free fatty acids; PPARα, peroxisome proliferator-activated receptor alpha; GLS, glutaminase; GPT2, glutamate pyruvate transaminase 2.

cal rate-limiting enzyme, providing another route to accelerate the glycolytic flux [50, 51].

N-glycosylation abnormality and activation of pentose phosphate pathway: Chronic stress-induced metabolic stress, such as a decrease in the glycolytic intermediate uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), interferes with N-glycosylation [52]. Abnormal glycosylation can alter the conformation of cell surface receptors (such as integrins), enhancing the interaction between tumor cells and the extracellular matrix, promoting invasion, and facilitating long-distance colonization [53] (**Figure 3**, integrin pathway beneath the nucleus). Additionally, chronic stress stimulates the diversion of glycolysis toward the pentose phosphate pathway, a metabolic shift that produces NADPH and nucleotides to mitigate stress-induced DNA damage and functional impairment [54].

Synergistic effect of metabolic intermediates on immune factors: Chronic stress modulates the expression of transfer-related genes through metabolic intermediates in glucose metabolism. For example, lactate inhibits histone deacetylases (HDACs), and the absence of HDAC activity induces EMT, thereby promoting metastasis [55, 56] (**Figure 3**, HDACs pathway). Lactate is pumped out by MCT4, leading to microenvironmental acidification, inhibition of T cell function, and recruitment M2 macrophages [57]. Moreover, the neuroendocrine-activated IL-6/STAT3 signaling pathway (as introduced in Section 4.1) upregulates PKM2, thereby promoting glycolysis and inhibiting the tricarboxylic acid (TCA) [58, 59] (**Figure 3**, STAT3/TCA pathway). This illustrates a specific mechanism by which the IL-6/STAT3 axis directly reprograms glucose metabolism in tumor cells.

Chronic stress affects lipid metabolism in tumor cells

Chronic stress affects the lipid metabolism of tumor cells through the neuroendocrine-immune regulatory system, promoting the imbalance of fatty acid synthesis, storage, and oxidation, thereby accelerating tumor growth and metastasis (**Figure 3**, ACTH/PPAR α pathway on the right). The following are the key mechanisms.

HPA and SNS system activation promote fat breakdown: Activated by chronic stress, the β-AR/cAMP/PKA pathway plays a direct role in lipid mobilization. It phosphorylates key lipases such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL), leading to the breakdown of lipid droplets and the release of free fatty acids (FFAs) [60, 61] (**Figure 3**, β-AR/CAMP pathway). These FFAs serve as an energy source and as building blocks for membrane synthesis in tumor cells. Concurrently, cortisol and NE promote the entry of fatty acids into mitochondria for oxidation by activating CPT1A through the PPARα/δ pathway, releasing ATP to support tumor proliferation [62, 63] (**Figure 3**, ACTH/CPT1A pathway).

Cortisol induces fatty acid synthesis: Chronic stress increases cortisol levels, which activate GR in tumor cells [64]. GR binds to SREBP-1c, upregulating the expression of fatty acid synthase (FASN), ACC,SCD1, thereby enhancing de novo lipogenesis (DNL) [65] (On the right side of **Figure 3**, Lipid regeneration pathway). Additionally, GR induces insulin resistance through IRS-1, forming a “cortisol-insulin resistance-lipotoxicity” cycle [66].

Immunoinflammatory co-regulation of lipid metabolism: Chronic stress-induced inflammatory factors (IL-6, TNF-α) enhance the expression of FASN through the STAT3 pathway, while inhibiting AMPK (a negative regulator of fatty acid oxidation) [67, 68] (**Figure 3**, STAT3/FAO pathway). TAMs, under stress, secrete IL-4/IL-13, activating the STAT6 pathway and promoting lipid uptake and storage in tumor cells [69, 70] (Above **Figure 3**, chronic stress/Lipid uptake and storage pathways).

Chronic stress alters the tumor microenvironment

The tumor microenvironment (TME) functions as the central processing unit of the triadic network, where signals from the nervous system and the gut microbiota converge to determine metastatic outcomes. The effects of chronic stress on the TME involves multiple levels: they are directly driven by neuroendocrine signals (Section 4.1) and are profoundly modulated by metabolites derived from both stressed tumor cells (Section 5.1) and the dysbiotic gut microbiota (Section 5.3).

T lymphocyte failure

Chronic stress disrupts adaptive immunity by altering T lymphocyte distribution and function. It increases CD11b+ Ly6C+ monocytes and decreases double-negative ($CD4^{-}CD8^{-}$) and double-positive (CD4+ CD8+) T cells, resulting in an imbalance of T lymphocyte subsets [71, 72]. Furthermore, it impairs T lymphocyte maturation and weakens their antigen-presenting ability [71]. Critically, the β-AR/cAMP signaling axis enhances the expression of the immune checkpoint protein PD-1 on T cells, thereby activating an immunosuppressive pathway and facilitating tumor immune escape [73, 74]. In conclusion, chronic stress reshapes the tumor microenvironment by altering T cell subsets, impairing immune cell function, and upregulating PD-1, collectively promoting immunosuppression and tumor progression.

Inactivation of NK cells

Studies have shown that chronic stress results in the continuous elevation of glucocorticoid levels through the abnormal activation of the HPA axis, inhibiting the secretion of IL-2, IL-12, and IFN-γ, and reducing the number of peripheral NK cells [75, 76]. Chronic stress also inhibits NK cell migration, cytotoxicity, and cytokine secretion by over-activating the SNS [77]. The synergy of these factors results in defects in the number and function of NK cells in the tumor microenvironment, increasing the risk of tumor metastasis.

Macrophage M2 polarization

Chronic stress can influence macrophage function in the tumor microenvironment by remodeling neuroendocrine and immunosuppressive signaling. Studies have shown that cortisol induces macrophages to express IL-10, promoting M2 polarization [78]. Additionally, β-AR activation induces macrophage polarization to the immunosuppressive M2 phenotype, and chronic stress enhances the infiltration of CD68+ TAMs [79, 80]. These findings confirm that the tumor-promoting effect of chronic stress depends on neuroendocrine-driven phenotypic transformation of macrophages.

Formation of neutrophil NETs

Under chronic stress, neutrophils reshape the tumor microenvironment by regulating the formation of NETs, thereby promoting tumor metastasis. Evidence shows that NETs can directly stimulate tumor cell migration and activate dormant cancer cells [81]. In addition, Within the TME, NETs release ROS that damage mitochondrial function and secrete proteases that degrade the ECM, easing cancer cell invasion [82] (**Figure 4**, NETs/ECM pathway). Confirmed the dual role of NETs in stress-induced metastasis progression.

Changes in microenvironment components

The changes in the tumor microenvironment are primarily reflected in the damage to the extracellular matrix (ECM) caused by chronic stress, alterations in the types and quantities of cytokines, and enhanced angiogenesis.

ECM damage: Chronic stress regulates the degradation of the extracellular matrix by activating the HPA axis and SNS, leading to the release of stress hormones. For example, norepinephrine and epinephrine upregulate matrix metalloproteinases (MMP-2/9) and urokinase plasminogen activator (uPA) through the β-AR signaling pathway, promoting ECM degradation and forming pathways for tumor invasion [83] (**Figure 4**, LPS/UPA pathway). Chronic stress also regulates changes in ECM rigidity, promoting the deposition and cross-linking of type I/III collagen via TGF-β and IL-6, which forms bridges in the basement membrane and facilitates cancer cell invasion [84].

Cytokine secretion: Chronic stress alters cytokine secretion and function within the tumor microenvironment through neuroendocrine and immune regulation. For example, activation of the HPA axis and SNS leads to the release of glucocorticoids and catecholamines, which in turn reduce IFN-γ secretion, thereby inhibiting the anti-tumor immune response [85, 86]. Additionally, this activation upregulates the expression of transforming growth factor-β receptor type II (TGF-β receptor type II) in ovarian cancer cells [87]. This enhanced receptor signaling can activate the canonical EMT pathway (as detailed in Section 3.2.1), thereby promoting metastasis.

As a core inflammatory pathway, the IL-6/STAT3 axis is potently activated by chronic stress (Section 4.1) and functions as a master regulator of immunosuppression. It enhances PD-1

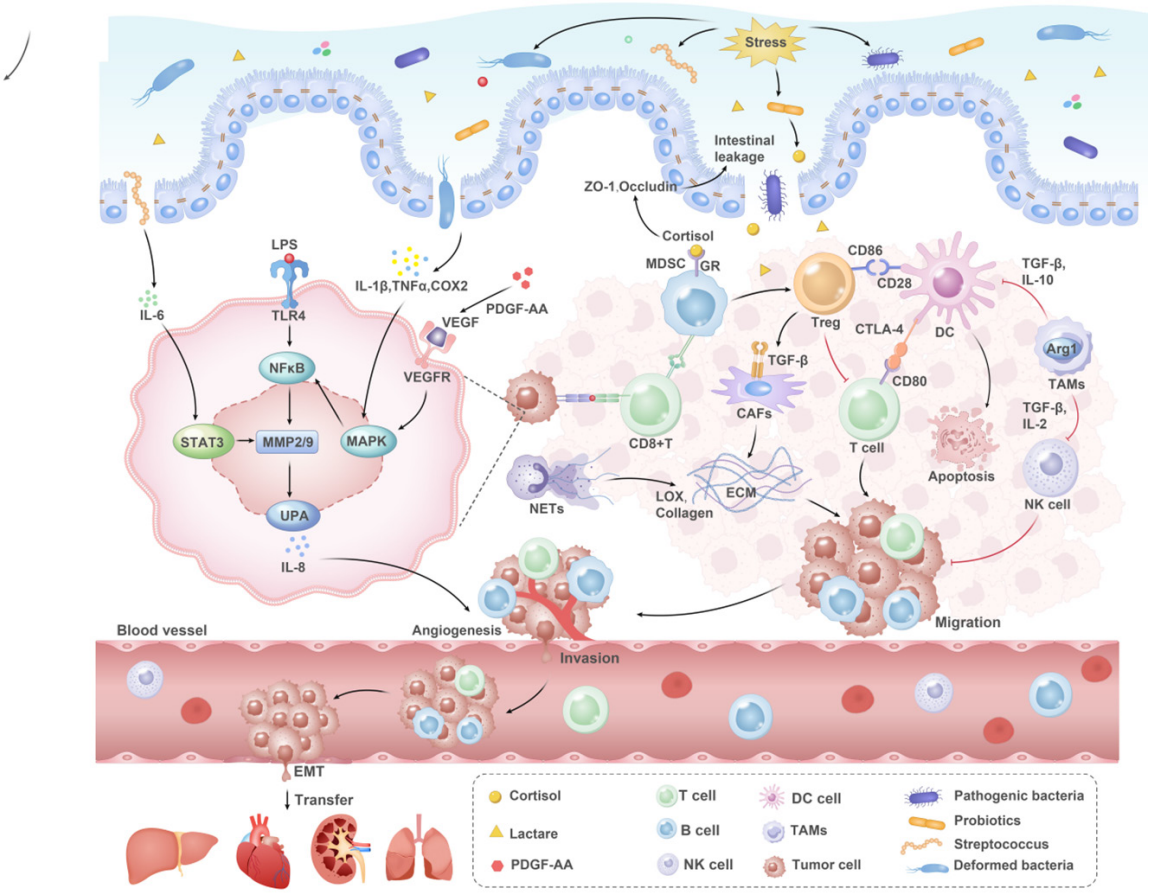

Figure 4. Chronic stress alters the TME and intestinal microbiota. Chronic stress modifies key components of the TME - including immune cells, extracellular matrix, cytokine networks, and angiogenic signaling - while impairing intestinal barrier integrity and microbial composition. These changes facilitate tumor dissemination and immune suppression. Chronic stress leads to an imbalance in the gut microbiota, with a decrease in beneficial bacteria and an increase in harmful bacteria. This dysbiosis impairs intestinal barrier function, leading to intestinal leakage. Consequently, bacterial components such as lipopolysaccharides (LPS) enter the bloodstream and activate immune cells, primarily through Toll-like receptor 4 (TLR4), which triggers the NF-κB and STAT3 signaling pathways. This activation promotes the expression of inflammatory factors, including IL-6, IL-1β, TNFα, and COX2, which further promote tumor cell proliferation and survival. These inflammatory factors promote tumor angiogenesis and invasion by stimulating endothelial cells (ECs) to express VEGF and PDGF-AA, forming new blood vessels, while concurrently activating cancer-associated fibroblasts (CAFs) to secrete matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (uPA), which degrade extracellular matrix (ECM) and promotes tumor cell invasion and metastasis. In addition, chronic stress creates an immunosuppressive environment in the TME by increasing the accumulation of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which secrete IL-10 and transforming growth factor beta (TGF-β) to inhibit the activity of effector T cells and natural killer cells (NK cells), thereby suppressing anti-tumor immune responses. Simultaneously, dendritic cells (DCs) within the TME are functionally impaired and cannot effectively present tumor antigens, further weakening the immune response. *The figure was created using Adobe Illustrator. Abbreviations*: IL-6, interleukin 6; TNFα, tumor necrosis factor alpha; IL-2, interleukin 2; IL-10, interleukin 10; IL-1 beta, interleukin-1β; TAMs, tumor-associated macrophages; HIF-1α, hypoxia-inducible factor 1 alpha; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor kappa B; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; MMP2/9, matrix metalloproteinase 2/9; uPA, urokinase-type plasminogen activator; MAPK, mitogen-activated protein kinase; COX2, cyclooxygenase 2; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PDGF-AA, platelet-derived growth factor AA; ZO-1, zonula occludens-1; MDSC, myeloid-derived suppressor cells; NETs, neutrophil extracellular traps; LOX, lysyl oxidase; ECM, extracellular matrix; CAFs, cancer-associated fibroblasts; TGF-β, transforming growth factor beta; CTLA4, cytotoxic T-lymphocyte-associated protein 4.

expression on T cells and promotes M2 macrophage polarization [73]. Furthermore, β-AR activation facilitates the recruitment of TAMs through neuropeptide Y (NPY), synergistically increasing IL-6 levels, thereby aggravating the inflammatory response and contributing to

immunosuppression [88]. The IL-6/STAT3 axis exemplifies the convergence within the network: it is activated by neural signals (catecholamines), amplified by immune cells (TAMs), and can itself be sustained by inflammatory signals originating from the gut, thus integrating inputs from all three network components.

Angiogenesis: Activation of β-AR by catecholamines is a primary mechanism through which chronic stress directly drives the expression of angiogenic factors, most notably VEGF [34, 89]. β-AR signaling also upregulates the expression of matrix metalloproteinases MMP-2 and MMP-9, platelet-derived growth factor AA (PDGF-AA), epithelial neutrophil-activating peptide 78 (ENA-78), and angiopoietin. These factors promote angiogenesis and extracellular matrix degradation, thereby creating a microenvironment conducive to metastasis [89, 90] (**Figure 4**, VEGF/UPA pathway).

Furthermore, chronic stress enhances VEGF signaling sensitivity and efficacy through the VEGF receptor (VEGFR2). Activation of the plexinA1/VEGFR2-Janus Kinase 2 (JAK2)-Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathway amplifies cellular responses to VEGF, thereby promoting angiogenesis [91, 92] (**Figure 4**, STAT3/UPA pathway). This demonstrates a convergence where the pro-angiogenic VEGF signal is potentiated by the JAK2/STAT3 module, which is also central to inflammation and immune regulation. However, chronic stress-induced overproduction of these factors can disrupt vascular network formation and induce metabolic disorders in the tumor microenvironment, such as acidosis and hypoxia. These conditions further promote tumor metastasis [93, 94].

Chronic stress changes intestinal flora

The gut microbiota functions as a systemic modulator and amplifier of the triadic network. Chronic stress disrupts the intestinal barrier function and causes microbial imbalance [95, 96]. Initially driven by neuroendocrine signaling, this dysbiosis subsequently feeds back into the network by releasing pro-metastatic metabolites and propagating systemic inflammation that reshapes the distal TME. Below, we summarize the three core mechanisms (**Figure 4**).

Destroy the intestinal barrier and promote tumor cells to enter the circulatory system

Chronic stress leads to the loss of tight junction proteins and damage to the microvilli structure, impairing the intestinal mucosal barrier [97]. In addition, the imbalance of intestinal flora allows lipopolysaccharide (LPS) to enter the bloodstream, activating the TLR4/NF-γ B inflammatory pathway. This results in the upregulation of MMP-2/9 and IL-8, d which degrade the basement membrane and facilitate tumor cells' entry into the circulatory system [98-100]. Moreover, the reduction of beneficial bacteria caused by microbial imbalance weakens the production of anti-inflammatory factors and diminishes mucosal repair capacity [101]. The destruction of physical and immune barriers significantly promotes tumor cells' entry into the circulatory system, establishing a pathological foundation for metastasis.

Metabolic product changes enhance tumor metastasis

Chronic stress can disrupt the balance of metabolic products in the gut microbiota, promoting cancer progression through EMT and angiogenesis [102]. For instance, chronic stress exacerbates neuroimmune inflammation, weakens intestinal mucosal immune function, and increases the abundance of microbial metabolites, such as gRuminococcaceae-UCG_014, which accelerates tumor metastasis [103]. Metabolites from specific bacterial strains have bidirectional regulatory effects. For example, enterotoxins produced by enterotoxigenic Escherichia coli (ETEC) downregulate VEGF/VCAM-1 through the cGMP signaling pathway, inhibiting metastasis, while quorum-sensing peptides produced by Bacillus subtilis, Streptococcus, and Escherichia coli promote angiogenesis and cancer cell invasion [103, 104].

Regulating microbiota immune disorders to promote metastasis

Chronic stress can activate pro-inflammatory pathways such as NF-κB and MAPK, disrupt the intestinal mucosal barrier, allow pathogens and toxins to enter the systemic circulation, and disturb the balance of gut microbiota [105]. Furthermore, the expansion of pro-inflammatory microbiota activates immune inflammation.

For example, an increase in the abundance of Proteobacteria leads to the overexpression of pro-inflammatory factors such as IL-1β, TNF-α, and COX-2 [106]. Additionally, an increase in inflammation-associated bacteria, such as Lactobacillus, Streptococcus, and Enterococcus, promotes colitis and a pro-tumorigenic state by activating the IL-6/STAT3 pathway [107]. This chronic, microbiota-driven activation of IL-6/STAT3 signaling in the host contributes to the systemic inflammatory and immunosuppressive microenvironment that favors tumor metastasis.

In summary, a self-reinforcing vicious cycle may be established in which the nervous system induces dysbiosis of the gut microbiota, leading to systemic inflammation and an immunosuppressive TME. This, in turn, exacerbates tumor progression and generates additional systemic pressure, and this cycle summarizes the dynamic and pathological properties of the ternary network.

The potential of targeting gut microbiota in cancer treatment

Given the gut microbiota's role as a central node in the triadic network, its targeted modulation represents a promising therapeutic strategy to disrupt the pro-metastatic cascade. Many studies have investigated the mechanisms and treatment strategies for microbiota-targeted interventions in cancer therapy. For example, in immune regulation, the gut microbiota enhances the activity of NKT cells through microbiota-mediated bile acid metabolism, thereby inhibiting cancer development [108]; SCFAs enhance the cytotoxic function of CD8+ T cells and the metabolic adaptability of CAR-T cells, improving tumor killing ability [109, 110]. Akermansia muciniphila and Microcysteinella have restored the anti-cancer effects of PD-1 blockade by amplifying T cell activity [111, 112]. In terms of barrier repair, probiotics provide energy to intestinal stem cells through glycolysis, alleviating the impact of chronic stress on internal balance, reducing intestinal inflammation, and enhancing intestinal barrier function [113].

Reports have also outlined tumor treatment strategies targeting the gut microbiota, such as combining gut microbiota with molecular targeted drugs to overcome the permeability and immune suppression barriers at cancer sites, which are challenges in traditional chemotherapy [114]. Additionally, modifying intestinal bacteria through gene editing to express specific proteins can create a targeted delivery system to regulate the composition, function, and metabolites of the local microbiota [115, 116].

Strategies to mitigate the impact of chronic stress on tumor metastasis

Physical and mental intervention measures

Physical and mental interventions can alleviate chronic stress and its associated health risks by regulating neuroendocrine function, immune function, and behavioral patterns. The main methods include psychological interventions, physical and mental relaxation training, social support, and traditional Chinese medicine (TCM) interventions [117, 118]. Research has shown that psychological intervention can inhibit metastatic non-small cell lung cancer induced by chronic stress through the β-AR activated cAMP signaling pathway [119]. Cognitive-behavioral stress management (CBSM) can alleviate psychological stress in patients with cancer, reverse the expression of anxiety-related pro-inflammatory genes, and reduce chronic stress levels [120, 121].

Physical and mental relaxation techniques are mainly regulated through yoga, music therapy, and mindfulness training. Yoga combines postures with breathing exercises to relieve stress and chronic inflammation [122, 123]. Music therapy improves mental health and alleviates psychological disorders such as anxiety and depression by engaging patients in music listening or activities [124]. Mindfulness training helps patients focus on their present experiences, reduce rumination, alleviate cancer-related pain and fatigue, and enhance their ability to cope with stress [125]. Social support reduces loneliness, depression, and anxiety in patients through participation in collective activities. It also improves immune function and lowers both all-cause and cancer-related mortality rates [126, 127]. In addition, acupuncture and moxibustion in TCM physical and mental interventions can treat depression and alleviate cancer-related pain, fatigue, and sleep disorders [128, 129]. Tai Chi practice has been shown to improve fatigue and soothe emotions [130].

Pharmacological intervention measures

Intervention targeting the SNS axis

Propranolol, a non-selective β-AR antagonist, inhibits the binding of NE released by the SNS to β 2-adrenergic receptors (ADRB2) on tumor cells, thereby suppressing tumor proliferation and metastasis [131, 132]. Carvedilol can inhibit NE-mediated angiogenesis and reshape the immunosuppressive tumor microenvironment [133]. Other adjuvant drugs, such as glutamate, can regulate both sympathetic and parasympathetic nerve activity, improve chronic stress-induced neuroendocrine disorders, and thus reduce the risk of tumor metastasis [134].

Intervention targeting the HPA axis

Propranolol and metoprolol can block the interaction between catecholamines and β-ARs, reversing NE-induced epithelial adhesion and inhibiting tumor proliferation and metastasis [131, 135]. β-AR blockade also enhances glycolysis and oxidative phosphorylation in tumor-infiltrating lymphocytes, increasing the expression of CD28 and boosting their anti-tumor function [136]. Additionally, propranolol inhibits β-AR activated VEGF and MMP-2/9 activation, blocking tumor angiogenesis and invasion [137]. Etifoxine can prevent excessive activation of the HPA axis induced by chronic stress [138].

Interventions targeting signaling pathways

Olanzapine can reverse anxiety-like behavior and lung cancer stemness induced by chronic stress by reducing NE synthesis and release, blocking the ADRB2-cAMP-PKA-CREB signaling pathway, and inhibiting neuronal activity in the medial prefrontal cortex (mPFC) under chronic stress [139]. Jiaotai Pill (JTW) exerts hypoglycemic and antidepressant effects by activating the cAMP/PKA/CREB signaling pathway [140]. Huangqi total flavonoids (TFA), resveratrol (RES), and amisulpride can alleviate chronic stress-induced depression through the Wnt/β-catenin pathway [141, 142]. Additionally, baicalin promotes hippocampal neurogenesis by regulating the Wnt/β-catenin signaling pathway, thereby exerting antidepressant effects [143].

Interventions targeting tumor metabolism

Xiaoyao San has been shown to improve abnormalities in amino acid metabolism, energy metabolism, and glucose metabolism in a rat model induced by chronic stress [144]. Oral administration of genipin significantly altered energy and glucose metabolism in the chronic stress treatment group [145]. Gynostemma pentaphyllum saponins (Gyp) inhibit the proliferation and migration of gastric cancer by reducing glucose uptake and utilization in cancer cells [146]. Additionally, Chaihu Shugan San can improve lipid metabolism changes and reduce prostate cancer metastasis caused by chronic stress [147].

Traditional Chinese Medicine intervention

Benzodiazepines are first-line drugs in the treatment of chronic stress-related diseases. However, long-term use of these drugs can lead to drug dependence, memory, and cognitive impairment, which limits their clinical application [148]. In contrast, TCM treatments offer the advantages of fewer side effects and a higher degree of individualization, making them highly valuable for clinical research. For example, JYHH capsules can counteract anxiety-like behavior induced by chronic stress by regulating monoamine neurotransmitters and the cAMP signaling pathway [149]. Gastrodin (GAS) activates the cAMP/PKA/CREB signaling pathway in hippocampal neurons, reducing stress-induced synaptic plasticity damage and behavioral dysfunction [150]. Xingpu Jiyu Tang improves depression and learning and memory disorders through the cAMP/PKA/CREB-BDNF signaling pathway [151]. Centella asiatica glycoside exerts antidepressant and anti-inflammatory effects in a chronic stress-induced mouse model by regulating the cAMP/PKA signaling pathway [152].

Discussion

Chronic stress, a complex and dynamic systemic pathophysiological state, promotes tumor metastasis through mechanisms distinct from traditional gene mutations or environmental carcinogenic factors. Unlike traditional factors that directly damage DNA or induce gene mutations to drive tumor development, chronic stress disrupts the delicate balance between neuroendocrine, immune, metabolic, and micro-

biome systems. It continuously reshapes the body's homeostasis, creating a complex signaling regulatory environment that includes neuroendocrine signals (such as β-adrenergic receptors and GRs), metabolic signals (such as the reprogramming of glucose and lipid metabolism), and microbiome signals (such as the interaction between the microbiome and the immune system). This ultimately allows tumor cells to break through the metastasis defense mechanisms, forming a more intricate metastatic process. In contrast to the irreversibility of genetic factors, chronic stress displays a degree of reversibility and intervention potential, and its pro-metastatic effects can even be partially reversed through psychological intervention or pharmacological treatment. Furthermore, chronic stress can directly impact tumor cells, the tumor microenvironment, and the gut microbiota through various inter-organ signaling networks, such as the brain-gut axis and sympathetic nervous system-immune axis. This results in a multi-target synergistic effect, deepening its role in promoting tumor metastasis.

The synergistic effect of nerves and microenvironment

The β-AR/cAMP/PKA signaling pathway, which becomes activated as a consequence of chronic stress, has the significant ability to directly upregulate the EMT in tumor cells, thereby promoting their invasive characteristics and impairing the functionality of immune cells that are crucial for the body's defense mechanisms. Furthermore, the stress-induced enhancement of glycolysis results in an increased accumulation of lactate within the tumor microenvironment, which in turn leads to a detrimental acidification of that environment. This acidic shift not only creates a hostile setting for immune cell activity but also activates matrix metalloproteinases (MMPs), enzymes that play a critical role in the breakdown of the ECM, thereby accelerating its degradation and facilitating tumor progression and metastasis. Accumulated lactate can also inhibit the function of CD8+ T cells. The evidence above links neural dysfunction to microenvironmental metabolic changes.

The interaction between the immune microenvironment and dysbiosis of microbiota

Chronic stress significantly disrupts the delicate intestinal barrier by inhibiting the expression of crucial tight junction proteins within the intestinal epithelium, which are essential for maintaining the integrity of this barrier. This disruption creates a pathway for microbial metabolites to enter the bloodstream, subsequently activating the NF-κB pathway, which leads to the release of various inflammatory factors. This cascade of events exacerbates immune suppression within the microenvironment, creating a vicious cycle of inflammation and immune dysfunction. Furthermore, the reduction of beneficial bacteria, a consequence of dysbiosis, can severely inhibit the function of regulatory T cells, which play a vital role in maintaining immune balance and tolerance. The compelling evidence presented above clearly links the dysfunction of the immune microenvironment to the dysbiosis of the microbiota, highlighting the intricate relationship between stress, gut health, and immune regulation.

Triadic interaction of neuro microenvironment microbiota

Activation of the neuroendocrine system can suppress immune function within the microenvironment and affect the balance of intestinal microbiota metabolites, while these metabolites, in turn, can stimulate neuroendocrine activity. Dysbiosis of the intestinal microbiota can exacerbate immune suppression in the microenvironment, and inflammatory factors within this environment can feedback to enhance metabolic abnormalities in tumor cells. Ultimately, this forms a positive feedback loop of neuroendocrine activation, microbiota imbalance, immune suppression, metabolic reprogramming, and inflammatory cascades, continuously driving the metastatic cascade reaction.

Current research has not fully elucidated the unique biological mechanisms through which chronic stress acts as an independent risk factor, nor clearly defined its interaction with traditional genetic and environmental contributors. Moreover, most existing studies focus on a single mechanism, such as stress-induced activation of tumor cell signaling pathways or microbiota dysbiosis, without systematically integrating the cross-organ, synergistic effects of the "neural microenvironment microbiota" axis. The absence of a unified theoretical framework for the "brain-gut-tumor" axis has resulted in fragmented mechanistic analyses.

For example, how chronic stress simultaneously regulates tumor cell metabolic reprogramming, microenvironment immune suppression, and gut microbiota dysbiosis through the HPA axis, and the key crossover nodes involved in this molecular network, remains unclear. Furthermore, no consensus exists regarding the efficacy of existing microbiota intervention strategies in reversing stress-related metastasis, and the potential impact of host microbiota co-evolution on treatment response has yet to be considered. As chronic stress-induced metastasis is a complex network process involving multiple mechanisms, single-target interventions are unlikely to provide comprehensive therapeutic benefit.

Future research should therefore focus on developing multi-target, combined intervention strategies. We hypothesize that a comprehensive approach combining "psychological intervention, pharmacological blockade, and microbiota regulation" would be more effective than single-factor interventions. Specifically, we propose using chronic variable stress (CVS)-induced tumor bearing animal models to investigate the synergistic effects of these combined interventions.

For pharmacological blockade, we suggest targeting key signaling pathways such as the HPA axis and the PI3K/Akt/STAT3 signaling, which are critically involved in tumor progression. For microbiota regulation, fecal microbiota transplantation (FMT) experiments should be conducted in these animal models to explore the potential of restoring a healthy microbiota composition to inhibit stress-related metastasis.

It is crucial to move beyond single mechanism perspectives and conduct multi-omics analyses, including genomics, transcriptomics, proteomics, and metabolomics, to capture the complex interplay underlying tumor metastasis. Future research should focus on further exploring the key interaction nodes of the "gut/brain/tumor" axis. Multi-omics approaches can be utilized to analyze the interactions between various pathways and identify key metabolites and signaling molecules involved in tumor progression. We further hypothesize that certain metabolites produced by the gut microbiota, such as SCFAs, may exert significant effects on the tumor microenvironment and immune responses. We propose conducting targeted metabolomics studies to identify these key metabolites and delineate their downstream signaling cascades. Combining bioinformatics methods to process large datasets will help identify these key interaction nodes. Moreover, the development of dynamic multi-omics monitoring techniques, paired with advanced detection technologies such as mass spectrometry and sequencing, will allow for regular testing on patient samples. This would facilitate the establishment of a comprehensive database to analyze and manage dynamically monitored data, offering real-time insights into molecular changes during the process of chronic stress promoting metastasis.

Finally, the development of personalized intervention strategies for patients experiencing chronic stress is essential. Given the heterogeneity in stress levels and physiological conditions among individuals, treatment plans should be tailored to optimize therapeutic precision and efficacy. We propose developing a personalized intervention algorithm based on patients' genetic profiles, metabolic conditions, psychological states, and other relevant factors. This algorithm could recommend specific combinations of psychological interventions (e.g., cognitive-behavioral therapy), pharmacological treatments (e.g., Traditional Chinese patent medicines and simple preparations therapy), and microbiota-based therapies (e.g., probiotics or personalized FMT). By evaluating these factors comprehensively, individualized interventions can be developed to provide more comprehensive and targeted care for patients with stress-related cancer progression.

Conclusion

This study systematically delineates how chronic stress promotes tumor metastasis via three interconnected mechanisms: directly enhancing tumor cell aggressiveness, remodeling the tumor microenvironment, and perturbing gut microbiota homeostasis. We further integrate these processes into a unified ternary network model, highlighting the synergistic interplay among neuroendocrine signaling, immune microenvironment remodeling, and microbial metabolism. Our findings illustrate that chronic stress orchestrates metastasis through sustained cascades involving endocrine dysregulation, microbial imbalance, metabolic adaptation, and immune-inflammatory activation, as summarized in **Figure 5**. Importantly, unlike genetic alterations, the pro-metastatic effects of chronic stress exhibit reversibility, revealing

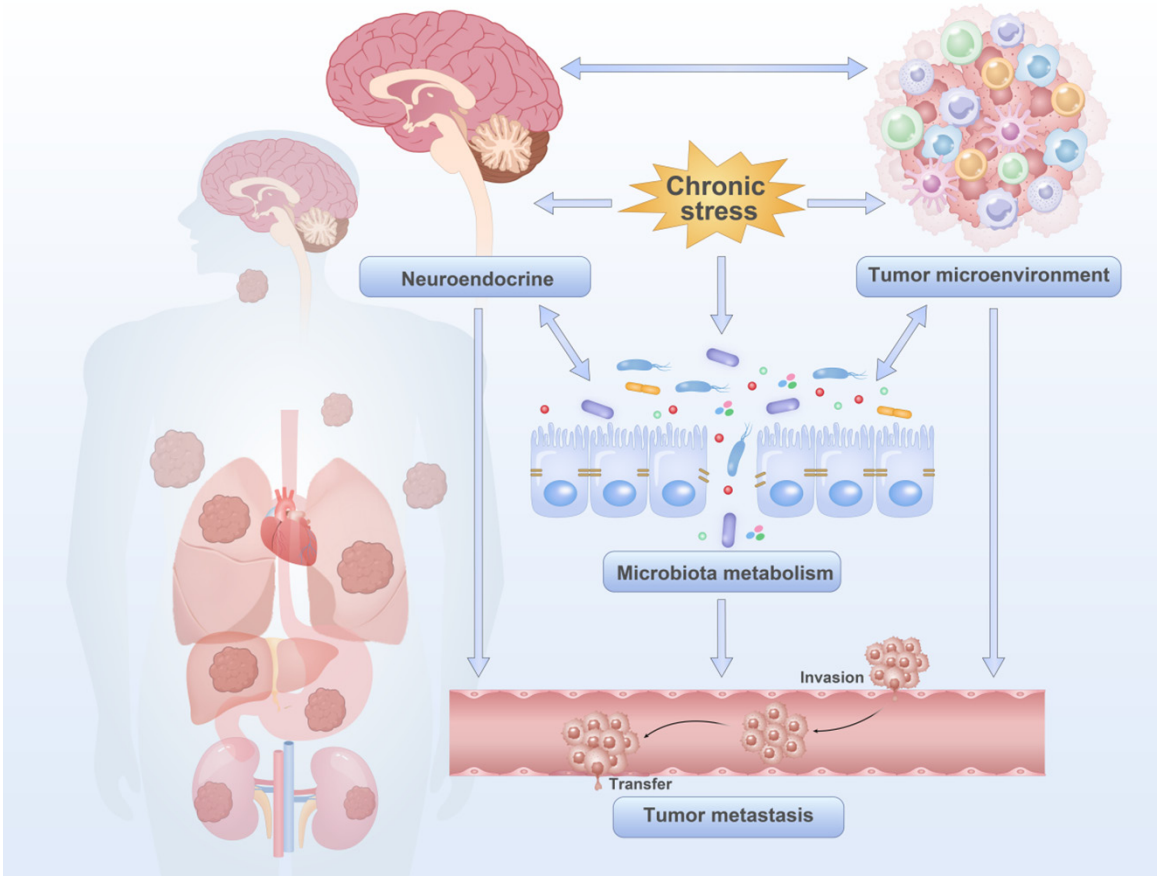

Figure 5. Chronic stress promotes tumor metastasis via the "neuro-microenvironment-microbiome" axis. A cascade of neuroendocrine activation, microbial dysbiosis, immune suppression, metabolic reprogramming, and chronic inflammation promotes tumor metastasis under chronic stress. This ternary regulatory network integrates neural, immune, and microbial signaling to sustain a pro-metastatic microenvironment. *The figure was created using Adobe Illustrator*.

unique potential for intervention through pharmacological or behavioral strategies.

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Glossary

Acetyl-CoA carboxylase (ACC), An enzyme involved in fatty acid biosynthesis, converting acetyl-CoA to malonyl-CoA; Acetylcholine (ACh), A neurotransmitter that modulates parasympathetic nervous system functions and may influence tumor progression; Adrenocorticotropic hormone (ACTH), A pituitary hormone that stimulates cortisol release from the adrenal cortex in response to stress; AMP-activated protein kinase (AMPK), A cellular energy sensor that regulates metabolism and inhibits tumor-promoting processes under stress; Arginase 1 (ARG1), An enzyme expressed by immune cells that can suppress T cell responses and promote tumor immune evasion; Adipose triglycer-

ide lipase (ATGL), An enzyme initiating lipid droplet breakdown, contributing to free fatty acid release in cancer metabolism; Bile acids (BAs), Steroid acids derived from cholesterol that can regulate gut microbiota and influence tumor-promoting inflammation; Beta-adrenergic receptor (β-AR), A stress-responsive receptor that mediates sympathetic nervous system effects and facilitates tumor metastasis; Brain-derived neurotrophic factor (BDNF), A neurotrophin that supports neuronal survival and may be involved in stress-related cancer signaling; Cancer-associated fibroblasts (CAFs), Stromal cells within the tumor microenvironment that promote cancer cell invasion and immune evasion; Cognitive-behavioral stress management (CBSM), A psychological intervention to reduce stress and its physiological impact on disease progression; Cyclic adenosine monophosphate (cAMP), A second messenger involved in many cellular signaling pathways, including β-AR-mediated stress responses; Cyclooxygenase-2 (COX2), An enzyme that promotes inflammation and angiogenesis, often upregulated in cancers; Corticotropin-releasing factor (CRF), A hypothalamic hormone that initiates the HPA axis stress response; cAMP response element-binding protein 1 (CREB1), A transcription factor activated by PKA in stress signaling, regulating gene expression in tumor cells; Carnitine palmitoyltransferase 1A (CPT1A), A mitochondrial enzyme that controls fatty acid oxidation, crucial for cancer cell energy metabolism; Cytotoxic T-lymphocyte-associated protein 4 (CTLA4), An immune checkpoint molecule that inhibits T cell activation and contributes to tumor immune escape; Deoxycholic acid (DCA), A secondary bile acid implicated in inflammation and colon cancer progression; De novo lipogenesis (DNL), The metabolic synthesis of fatty acids from non-lipid precursors, often upregulated in tumors; Extracellular matrix (ECM), A structural network of proteins and molecules surrounding cells, which is remodeled during tumor invasion and metastasis; Epithelial-mesenchymal transition (EMT), A process by which epithelial cells acquire mesenchymal traits, enhancing motility and invasiveness; Enterotoxigenic Escherichia coli (ETEC), A pathogenic bacterial strain known for producing toxins and altering host immune responses; Fatty acid β-oxidation (FAO), A metabolic pathway that breaks down fatty acids in mitochondria to produce energy, often hijacked by tumors; Fibroblast growth factor (FGF), A signaling molecule involved in tissue repair, angiogenesis, and tumor development; Free fatty acids (FFAs), Products of lipid metabolism that serve as energy sources for tumor cells; Fatty acid synthase (FASN), A key enzyme in lipid biosynthesis, overexpressed in many cancers to support growth and survival; Farnesoid X receptor (FXR), A nuclear receptor that regulates bile acid homeostasis and may modulate inflammation in cancer; Glucose transporter 1/3 (GLUT1/3), Membrane proteins that facilitate glucose uptake into cells; often overexpressed in tumors; Gut microbiota (GM), The community of microorganisms in the digestive tract that interacts with the host immune system and influences cancer; Glucocorticoid receptor (GR), A nuclear receptor that binds cortisol and modulates stress responses, metabolism, and immune activity in cancer; Histone deacetylase (HDAC), A class of enzymes that regulate gene expression by modifying chromatin structure, implicated in cancer progression; Hypoxia-inducible factor 1-alpha (HIF-1α), A transcription factor that responds to low oxygen levels, promoting angiogenesis and tumor survival; Hexokinase 2 (HK2), A glycolytic enzyme critical for cancer cell metabolism and survival under stress; Hypothalamic-pituitary-adrenal (HPA) axis, The primary neuroendocrine system activated by stress, influencing immunity, metabolism, and cancer; Interferon (IFN), A cytokine involved in antiviral and anti-tumor immunity; Interleukin (IL), A group of cytokines that modulate immune and inflammatory responses within the tumor microenvironment; Janus kinase 2 (JAK2), A tyrosine kinase involved in cytokine signaling and Signal transducer and activator of transcription (STAT) pathway activation in inflammation and cancer; Lactate dehydrogenase A (LDHA), A glycolytic enzyme that converts pyruvate to lactate, promoting cancer metabolism and immune suppression; Lipopolysaccharide (LPS), A bacterial endotoxin that triggers immune activation via TLR4, contributing to tumor inflammation; Matrix metalloproteinases (MMPs), Enzymes that degrade ECM components and facilitate cancer cell invasion; Mechanistic target of rapamycin (mTOR), A central regulator of cell growth, metabolism, and survival, frequently activated in cancer; Neutrophil extracellular traps (NETs), DNA and protein structures released by neutrophils that can trap patho-

gens but also promote metastasis; Natural killer (NK) cells, Innate immune cells that can recognize and destroy tumor cells without prior sensitization; Peroxisome proliferator-activated receptor α/δ (PPARα/δ), Nuclear receptors that regulate lipid metabolism and inflammation; Programmed cell death protein 1 (PD-1), An immune checkpoint receptor that downregulates immune responses, exploited by tumors to avoid detection; Prostaglandin E2 (PGE2), A lipid compound involved in inflammation and tumor immune evasion; Pentose phosphate pathway (PPP), A metabolic route that provides NADPH and nucleotides, supporting cancer cell survival; Reactive oxygen species (ROS), Chemically reactive molecules that can damage cellular components and modulate cancer signaling pathways; Short-chain fatty acids (SCFAs), Microbial metabolites that influence immune regulation and tumor progression; Sympathetic nervous system (SNS), A branch of the autonomic nervous system activated by stress and involved in tumor progression via β-AR signaling; Signal transducer and activator of transcription (STAT), A family of transcription factors activated by cytokines and growth factors in tumors; Tumor-associated macrophages (TAMs), Macrophages in the tumor microenvironment that often adopt a tumor-promoting, immunosuppressive phenotype; Transforming growth factor beta (TGF-β), A cytokine that regulates cell proliferation and EMT, commonly hijacked in cancer; Toll-like receptor 4 (TLR4), A pattern recognition receptor that detects bacterial components like LPS and activates inflammation; Tumor microenvironment (TME), The cellular and molecular environment surrounding tumor cells, including immune and stromal components; Tumor necrosis factor alpha (TNF-α), A pro-inflammatory cytokine that can promote or inhibit tumor development depending on context; Uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), A sugar nucleotide involved in glycosylation, influencing tumor cell signaling; Urokinase-type plasminogen activator (uPA), A serine protease that facilitates ECM degradation and cancer cell invasion; Vascular cell adhesion molecule-1 (VCAM-1), A protein that mediates leukocyte adhesion and may contribute to cancer metastasis; VEGF, A potent angiogenic factor essential for tumor vascularization; Zinc finger E-box binding homeobox 1 (ZEB1), A transcription factor that promotes EMT and tumor progression; Zonula occludens-1 (ZO-1), A tight junction protein essential for maintaining intestinal barrier integrity, often disrupted by stress.

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