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Effects of chronic stress stimulation on the occurrence and development of tumors and the regulatory role of Chinese medicine

Wenqin Guo[1*] and Rongzhen Shi[2]

[1]College of Basic Medical Science, Zhejiang Chinese Medical University, 310053, Hangzhou, P.R. China

[2]Linping district traditional Chinese medicine hospital tangqi branch, 310053, Hangzhou, P.R. China

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***Correspondence**

Wenqin Guo, College of Basic Medical Science, Zhejiang Chinese Medical University, 310053, Hangzhou, P.R. China

E-mail: gwqjxnc@126.com

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Abstract

Chronic stress refers to the continuous non-specific adaptive response of the body caused by the activation of the classic hypothalamic-pituitary-adrenal axis neuroendocrine system and sympathetic nervous system, which not only affects sleep quality, appetite, and gastrointestinal function, but also increases the risk of atherosclerosis, cardiovascular disease, mental disorders, and tumors. Notably, chronic stress has been confirmed to induce tumorigenesis and promote tumor evolution, especially on the immune function of the body and the remodeling of the tumor microenvironment. Therefore, it is essential and important to improve the emotional disorders caused by chronic stress stimulation in cancer patients. Many studies have proved that traditional Chinese medicine and compound regulation can significantly improve anxiety, depression and tumor development in patients. In this article, the mechanism of CUMS affecting tumor and the therapeutic effect of traditional Chinese medicine compound are reviewed, so as to provide reference for the adjuvant treatment of cancer by traditional Chinese medicine.

1 Introduction

Chronic stress can weaken psychological and physical health, exacerbate disease progression, and especially exert serious adverse effects on the development of malignant tumors and the remodeling of tumor microenvironment (TME) [1-2]. Its effects on inducing tumorigenesis and facilitating the progression of tumors have been revealed in recent studies [3]. During the occurrence and development of tumors, tumor cells/tumor stem cells with stromal cells and components of extracellular matrix around vessels are interacted with each other, forming a complex microenvironment–tumor microenvironment (TME). Main characteristics of TME are acid environment, hypoxia, high levels of reactive oxygen species (ROS) and reducing substances, immunosuppression, etc. In general, slightly acidic environment is contributive to the metastasis of tumors, hypoxia can boost the drug resistance of tumors, the increased levels of ROS and reducing substances are beneficial to the treatment of tumors, and immunosuppression can promote the immune escape of tumor cells. Notably, Chinese medicine can effectively adjust emotions, and improve the prognosis as well as life quality of tumor patients, which is contributive to the prevention and treatment of malignant tumors, the prolongation of survival time, and the improvement of life quality. This article reviews the way of chronic stress to promote the tumorigenesis and progression and the therapeutic effect of Chinese medicine, so as to provide a reference for Chinese medicine treatment of tumors under chronic stress stimulation.

2 The mechanism of chronic stress stimulation on tumors

2.1 Neuroendocrine system

2.1.1 Hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid (GC)

Chronic stress can promote the tumorigenesis and progression through the neuroendocrine system. In neuroendocrine system, two branches of pathways, HPA axis and sympathetic nervous system (SNS), are first detected to be closely associated with chronic stress. HPA axis is mainly responsible for the secretion of GC. Chronic stress can stimulate hypothalamus to release corticotropin releasing hormone (CRH), and CRH can activate pituitary to release adrenocorticotropic hormone (ACTH), thereby stimulating adrenal cortex to boost the production and release of GC [4]. TME can regulate GC and GC receptors via its abundant cytokines and growth factors, thereby affecting the development of tumors. For instance, GC/receptor tyrosine kinase-like orphan receptor 1 (ROR1) can facilitate the deterioration and metastasis of breast cancer, and induce the progression of ovarian cancer as well as chemotherapy resistance [5]. Also, the increase of GC level can induce serum and glucocorticoid regulated kinase 1 (SGK1) to reduce the level of tumor suppressor protein P53 and then activate the function of murine double minute 2 (MDM2) by elevating its level, which can boost the formation of tumors to a great extent [6]. Additionally , during an in vivo mouse experiment under chronic stress simulation, it has been found that elevated GC level can enhance the conduction of tumor-associated macrophage (TAM)/C-X-C motif chemokine ligand 1 (CXCL1) signals, subsequent to which myeloid-derived suppressor cells (MDSCs) are recruited in the spleen to promote the formation of ecological niche before the metastasis of breast cancer through CXC chemokine receptor 2 (CXCR2) [7].

2.1.2 SNS and catecholamine

Chronic stress can stimulate SNS to release vital neurotransmitters such as catecholamine. Catecholamine includes norepinephrine (NE), epinephrine and dopamine (DA). NE and GC can bind with corresponding receptors in TME to stimulate the secretion of cytokines, repress immune response, and promote the angiogenesis as well as invasion of tumors. Besides, chronic stress induces the activation of epinephrine to enhance the metabolic activity of lactic acid by up-regulation of lactate dehydrogenase A (LDHA) and usp28, stabilize SLUG promoter, and boost the development of breast cancer stem cell-like properties [8]. NE can activate Notch1 signaling

pathway to enhance the malignant biological behaviors of pancreatic ductal adenocarcinoma, mediate the cell autophagy through AMPK/ULK1 pathway to propel the progression of gastric cancer, and provide nutrients for the growth of tumors [9]. In addition, chronic stress is able to regulate epithelial-mesenchymal transition (EMT) of cancer cells by activating β-adrenergic receptor (β-ARs), and promote the invasion and metastasis of cancer cells [10-11]. Inhibitors of β-ARs can hamper the anti-cancer effects of β-ARs in cancer tissues and promote the survival rate of cancer patients [12]. Under chronic stress, DA depletion provides a loose microenvironment for tumor growth, while dopamine receptor D2 (DRD2) overexpression is associated with advanced breast cancer and poor prognosis of patients with this disease [13].

2.2 Immune system

Chronic stress can promote inflammation and interfere with cell immunity to weaken the anti-tumor immune function of the body. In chronic unpredictable mild stress (CUMS)-induced mouse models, it was discovered that ABL proto-oncogene 1 (ABL1) activated by ROS could regulate inflammatory TME to facilitate the development of gastric cancer and depression related to gastric cancer. Besides, cytokines are tightly associated with the degree of depression and anxiety in patients with breast cancer [14]. The more serious the depression of patients is, the higher the level of plasma interleukin (IL)-6 is. Inversely, the level of anti-inflammatory factor IL-10 is significantly lower than in the normal people [14]. Under chronic psychological stress, the abilities of T cells to proliferate and differentiate are weakened, leading the imbalance of Th1/TH2 cells and the impaired immunity ability [15]. Also, catecholamine has unveiled to suppress the functions of various immune cells such as natural killer cells and macrophages, recruit macrophages to the tumor tissues and induce the differentiation into M2 phenotypes [16]. The imbalance of Th1/Th2 cells induced by chronic stress can affect the ability of cells to produce interferon-gamma (IFN-γ) and reduce the level of IFN-γ in the blood, repressing the immune function of mice and increasing the risks of tumorigenesis and metastasis [17].

2.3 Intestinal flora

There is a substantial body of microorganism in human intestinal tract, which is a pivotal part of intestinal immune system, making a profound impact upon the tumorigenesis and progression. First of all, parts of pernicious bacteria are direct cancerogen, where Helicobacter pylori is class I carcinogen of gastric cancer. Next, dysbacteriosis may result in inflammation and immunosuppression. The lipopolysaccharide produced by intestinal bacteria in patients with chronic liver disease boosts the liver inflammation and fibrosis through Toll-like receptors [18]. Bacillus enterotoxin generated by enterotoxin bacteroides can promote the differentiation of immature myeloid cells into MDSCs and repress the proliferation of T cells [19]. Also, intestinal flora can affect human central nervous system by microbiota-gut-brain axis, where secondary bile acid, a metabolite of intestinal flora, has been uncovered to promote the infiltration and metastasis of cancer cells as well as propel the tumorigenesis and progression [20]. Besides, some metabolites such as butyrate and short-chain fatty acid can penetrate the blood-brain barrier to affect the central nervous system [21], and neurotransmitters like 5-hydroxytryptamine can be generated in intestinal tract to directly impact the nervous system. Apart from these, the imbalance of emotions can also make alterations in the construction of flora, and lead to the down-regulation of beneficial bacteria as well as up-regulation of pernicious bacteria, thereby broking intestinal homeostasis [22]. Thus, intestinal flora is an important material basis of emotional factors to affect the tumorigenesis and progression.

2.4 Oxidative stress

Oxygen radical has toxicity to cells, tissues and bodies, the accumulation of which can lead to chain reactions. Namely, oxidative stress can impair macromolecular substances such as lipids, proteins, and nucleic acids.

Chronic stress can induce oxidative stress in the body. Several studies have discovered that the degree of depression in patients with breast cancer is positively related to the levels of oxidative stress markers [23], where the higher the psychological stress is, the higher the levels of oxidative stress markers are [24]. Typically, oxygen-deficient environment is a vital feature of tumors, which induces the metabolic reprogramming of tumor cells. This mechanism is mediated by hypoxia-inducible factor-1 (HIF-1), and reactive oxygen can activate the transcription of HIF-1 and boost its expression [25]. Abnormal emotions can induce oxidative stress response to impair normal cells and provide an appropriate environment for tumor growth via oxidative stress. Hence, emotional factors are an essential mechanism for the tumorigenesis and progression.

2.5 Metabolic abnormalities

Chronic stress can make alterations in metabolic functions of the body to promote the growth of tumor cells. Glycolysis is a typical metabolic way for tumor cells. A research has found that chronic stress can activate leptin receptor (LepR)-signal transducer and activator of transcription 3 (STAT3)/phosphatidylinositol 3-kinases (PI3K) signaling pathway in arcuate nucleus of rat hypothalamus, resulting in the increased susceptibility to glucose intolerance and the elevated fasting blood glucose [26], where high level of glucose provides raw material for the glycolysis of cancer cells. Chronic psychological stress up-regulates the expressions of key enzymes related to glycolysis, such as hexokinase 2 and LDHA [27]. The patients with emotional imbalance are prone to be crapulent and consume foods with high fat and calories, yet excess cholesterol will increase the risk of breast cancer, and its metabolite 27-hydroxycholesterol can stimulate the growth and metastasis of breast cancer cells MCF-7 [28]. In addition, adipose tissue can produce estrogen to raise the risk of cancers in obese women. Table 1 displayed the mechanism.

3 The regulation of Chinese medicine on the progression of tumors under the stimulation of chronic stress

The treatment of Chinese medicine is based on syndrome differentiation, with the merits of rapid absorbance and high efficacy. The literatures on the treatment of chronic stress-induced tumor progression with Chinese medicine in recent years can be summarized into three categories, namely dispersing stagnated liver qi to relieve depression, nourishing blood for tranquillization, as well as regulating the flow of qi to eliminate phlegm.

3.1 Dispersing stagnated liver qi to relieve depression

It has been found that the connection of the liver controlling conveyance and dispersion with emotions lies in the nerve-endocrine-immune system. The essence of smoothing emotions is mainly to regulate the secretion of substances such as central neurotransmitters and hormones during emotional abnormalities; these substances can act on hippocampus at multiple levels and targets, and negatively feed back to HPA axis, which integrates into different emotions through the cerebral cortex [29]. Sini powder (one kind of TCM can regulate liver and spleen) has been uncovered to restore the impaired hippocampal neuron, repress excess autophagy, and ameliorate depression-like behaviors [30]. In traditional Chinese medicine, it is believed that the liver interacts with the spleen. The stagnation of liver qi will affect the liver's function of controlling conveyance and dispersion, which will further impact the spleen's function of transporting and transforming nutrients, leading to spleen deficiency. Hence, soothing the liver and strengthening the spleen are the basic therapy. In tumor patients with different symptoms, the modified Chaihu Shugan powder (one kind of TCM can relieve liver-qi) has been uncovered to repress the progression of tumors and improve the depression at the same time [31]. Also, Fan Dahua et al. compared the anti-depression effects of Chaihu Shugan powder and western medicine fluoxetine, and found that Chaihu Shugan power could improve the depression-like behaviors of depression model rats

with liver-qi stagnation [32]. In addition, the modified Xiaoyao Powder (a classic anti-depression TCM) can significantly optimize the level of T lymphocyte subsets and neurotransmitters in menopausal breast cancer patients with depression after chemotherapy, and improve the clinical efficacy [26]. In another research, 96 patients with liver-qi stagnation has been selected and administrated with Fuzheng Kangfu mixture (observation group) or escitalopram oxalate tablets (control group); in observation group, the total effective rate is significantly increased to 93.75%, yet the Hamilton Depression Scale (HAMD) score is obviously reduced, as compared with those in control group [33].

Table 1 The mechanism of chronic stress stimulation on tumors

Influence	Mechanism	Effects on cancer	References
Neuroendocrine system	activate GC/ROR1 signals	facilitate the deterioration and metastasis of cancer	[5]
	induce SGK1 to reduce the level of P53 and activate the function of MDM2	boost the formation of tumor	[6]
	activate TAM/CXCL1 pathway	promote the formation of ecological niche before the metastasis of cancer	[7]
	enhance the metabolic activity of lactic acid, stabilize SLUG promoter	boost the formation of tumor	[8]
	activate Notch1 signaling pathway	enhance the malignant biological behaviors of cancer	[9]
	activate AMPK/ULK1 pathway	provide nutrients for the growth of tumor	[9]
	activate β-ARs	promote the invasion and metastasis of cancer cells	[10-11]
Immune system	the abilities of T cells to proliferate and differentiate are weakened, leading the imbalance of Th1/TH2 cells	immunity ability decrease	[15]
	affect the ability of cells to produce IFN-γ	increase the risks of tumorigenesis and metastasis	[17]
	activate Toll-like receptors	result in inflammation	[18]
Intestinal flora	promote the differentiation of immature myeloid cells into MDSCs and repress the proliferation of T cells	result in inflammation and immunosuppression	[19]
	increase metabolite of intestinal flora	propel the tumorigenesis and progression	[20]
Oxidative stress	induces the metabolic reprogramming of tumor cells	propel the tumorigenesis and progression	[25]
Metabolic abnormalities	activate LepR-STAT3/PI3K pathway	provide raw material for the glycolysis of cancer cells	[26]
	product excess cholesterol	increase the risk of cancer	[28]

3.2 Nourishing blood for tranquillization

If the depression of tumor patients can't be relieved

effectively in the long term, the qi and blood in the heart will be impaired, leading to the malnutrition of heart. Therefore, the therapeutic emphasis should be put on benefiting heart qi and nourishing blood for tranquillization. After treatment of supplemented Ganmai Dazao decoction, the total effective rate is elevated to 85%, the HAMD score is markedly diminished, with obvious efficacy and few adverse reactions [34]. Relevant research has shown that supplemented Ganmai Dazao decoction can improve the levels of T cell subsets and natural killer cells to ameliorate the immune functions of patients [35]. In addition, Guipi decoction has the effects of benefiting qi and strengthening the spleen, as well as nourishing blood and heart, which can signally reduce HAMD score and tumor necrosis factor alpha (TNF-α) level, as well as improve the Quality of Life Inventory (QOL) score [36]. Furthermore, a research has found that Xiegan Anshen decoction can significantly improve sleep quality, markedly relive the anxiety and depression as well as promote the memory of patients to some extent [37].

3.3 Regulating the flow of qi to eliminate phlegm

Lin Zhaoqiang believed that Liujunzi decoction, which has the effects of resolving phlegm and depression as well as benefiting qi and strengthening the spleen, could effectively adjust the middle energizer for promoting qi activity in patients with depression, and restore the spleen and stomach's ascending and descending functions, thereby invigorating qi and enriching the blood as well as nourishing the heart to calm the mind. More significant efficacy is found in the treatment of Liujunzi decotion in combination with Banxia Houpu decoction that has the effect of resolving phlegm and lowering the adverse qi, where the declined HAMD score signifies the improvement of depression. In addition, another research has shown that the combined therapy of Liujunzi decoction with Banxia Houpu decoction can conspicuously reduce SAS and SDS scores in gastric cancer patients with emotional dysregulation [39]. Also, Tiaoqi Anshen decoction can effectively improve the manifestations such as reduction of autonomic activities and susceptibility of irritation, raise the content of 5-HT and decrease the levels of DA and NE in brain tissues of depression model rats [40]. Moreover, Huatan Liqi oral liquid can ameliorate the anxiety and depression, as well as reduce the systemic inflammatory response syndrome of patients [41].

4 Conclusion

In traditional Chinese medicine, the imbalance of emotions is a vital cause of tumorigenesis. Also, epidemiology has verified that chronic stress boosts the umorigenesis and progression, and significantly impairs the prognosis and life quality of patients. Research has uncovered that emotions can affect tumors from aspects such as neuroendocrine, immune, intestinal flora, oxidative stress, metabolism, etc. However, the mechanisms involved are very complex, and the experimental results are affected by multiple factors. Hence, it is necessary to establish a stable animal model, and take advantage of omics and big data analysis tools to explore biological laws and material basis of emotional abnormalities affecting tumors. In the treatment of emotional disorders, Chinese medicine has unique advantages. This article tightly connects the theory of emotional pathogenicity with modern biological research, and elucidates multiple approaches and biological laws of the emotional factors affecting the tumors, which provides a potential mechanism for the development of novel strategies to prevent and treat tumors, and simultaneously offers scientific evidence for the application of Chinese medicine in regulating the emotions of tumor patients.

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Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization: W.Q.G; Formal analysis: R.Z.S; Writing-riginal draft: W.Q.G; Writing-review and

editing: R.Z.S; All authors have read and agreed to the published version of manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Supplementary Material

Not applicable

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