

Explain the relationship between the theory of spleen viscera and the pathogenesis of malignant tumors from the perspective of system theory

Jin-Hui Zuo, Jun Chang, Min Zhong, Xin-Rong Wang, Hong-Xia Xie, Dong-Ying Liao, and Fan-Ming Kong

Abstract—The spleen visceral manifestation theory (SVMT) is formed under the simple holistic thinking mode of traditional Chinese medicine (TCM). It emphasizes the change of our organic function. And SVMT can make me to understand the basic characteristics and rules of the organic functional change and disease evolution of spleen (which is a complex giant system from a macroscopic view). However, the formation of SVMT is still in the stage of fuzzy deduction, ignoring the structural basis of its function. As a result, although SVMT has a macroscopic accuracy, it is unable to analyze the internal structure from the perspective of reductionism. The systematic thought of unifying reductionism and holistic dialectics provides the possibility for the relationship between traditional Chinese medicine (TCM) theory and modern scientific research. Based on the systematic relationship between spleen storage and malignant tumor, this paper tries to take matter-energy-information as the starting point by drawing lessons from complex scientific theory and using the method of interdisciplinary comprehensive analysis under the guidance of system theory. Explore its mechanism and law more scientifically from the subcellular level, so as to further improve and deepen the theoretical system of malignant tumor research based on SVMT.

Key words—System theory, Spleen viscera manifestation theory, Malignant tumor

INTRODUCTION

The spleen viscera manifestation theory (SVMT) of traditional Chinese medicine (TCM) is the fundamental description of the life function and structure. In TCM, the five Zang-viscera refers collectively to heart, spleen, lung, liver and kidney. The spleen, as the mother of the five viscera, could provide a proper basis for acquired constitution, command blood, and source of phlegm. SVMT is committed to macroscopically explaining the physiological function and regulation mechanism of the five internal organs. It is of great significance to study the theory of visceral manifestation, especially SVMT. The spleen soil "occupies the center, irrigates the four sides, unifies the five internal organs", turns the lifting hub of the spleen and stomach, and opens and closes the circulation of ascending and descending qi. The tumor is caused by the

comprehensive stimulation of internal and external evil qi to the body, resulting in disorder of rising and falling of qi, and struggle of phlegm, dampness, poison and blood stasis. The imbalance with the "main movement and transformation" of the spleen as the core is the essence of the disorder of elements such as spirit, subtlety, qi and blood, body fluid and so on. To deduce the disordered physiological function by the method of "thinking outside and inside" in TCM is the embodiment of the thinking of TCM. Under the outline of the interrelation of heaven, earth and man, the theory of spleen viscera accurately describes the changes of the functional level of the diseased body macroscopically and accurately, but the vague understanding can only barely explain the changes of function and fails to elaborate the mechanism of Zang-fu organs in detail and systematically from the level of structure. Therefore, SVMT formed under the background of not seeing the internal details and paying no attention to the study of microstructure has the defects of unclear location of diagnostic diseases and general treatment methods [1]. However, the traditional visceral image theory contains the thinking of systematic analysis. we find the opportunity for the development of the traditional visceral image theory from the modern system theory, and also provide a deeper study for SVMT to guide the differentiation and treatment of tumors.

MODERN SCIENTIFIC SYSTEM THEORY

System theory, which originated in the 1940s, is a combination of logic and mathematical nature [2]. Through the subtle decomposition of the structure of the human body, the reductionism of western medicine strives to explain the macroscopic phenomenon of life with the change of microstructure. This method of linearization and causality of life system is easy to lose a large amount of information in the one-way exploration of disconnection. It also ignores the description of the random, comprehensive and nonlinear characteristics of life phenomena and medical laws by system theory [3]. Modern system theory holds that the human body is not a mixture of organs, but a self-organized organic whole. System theory is the dialectical unity of holism and reductionism, and it is a scientific and high-level holistic view. System theory advocates the analysis of body changes from the point of view of integrity, interconnection, order, dynamics, hierarchy and self-organization, which is not only an in-depth analysis and comprehensive induction of the concept of integrity, but also the ideological basis for the development of integrated medicine in the future.

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THE PRESENT SITUATION AND FUTURE DEVELOPMENT TREND OF SPLEEN VISCERAL IMAGE THEORY

The theory of spleen visceral image is the integration of the processes of digestion, absorption, transportation, transformation and unification of blood, as well as a high summary of the complex and intertwined network system of integrity, function, spleen and spirit, spleen and essence, qi and blood, body fluid and so on. Spleen soil in the center, irrigation four sides, derived from the "five internal organs have temper, regulate the spleen to calm the five internal organs" clinical thinking. Traditional Chinese medicine advocates the therapeutic view of "seeing the micro-knowledge and constantly changing", so the clinical research based on SVMT mostly takes "treating from the spleen" as the starting point to study different system diseases. To explore the "syndrome" of the same splenic dysfunction under different "symptoms" is a skillful application of SVMT. Traditional Chinese medicine has its own understanding of the pathogenesis of malignant tumor, but it is always related to the accumulation of phlegm, poison, blood stasis and turbid caused by the dysfunction of spleen and stomach. However, the understanding of the disease by the method of "governing exterior to infer interior" still stays in the simple "black-box deduction" stage, and the theory of spleen pathogenesis formed by black-box reasoning which does not have the conditions to open is vague and immature. In order to adapt to the development trend of integrated medicine, it is necessary to learn from the methods of complexity science and interdisciplinary comprehensive analysis, and take matter-energy-information as the starting point. the new scientific connotation of spleen visceral image theory and its pathogenesis changes under the guidance of the theory of spleen visceral image was explained by the combination of whole and reduction, macroscopic and microcosmic, qualitative and quantitative methods, so as to promote the theory of spleen visceral image from simplicity to modernity [4].

THE RELATIONSHIP BETWEEN SPLEEN VISCERAL IMAGE THEORY AND MALIGNANT TUMOR FROM THE POINT OF VIEW OF SYSTEM THEORY

Spleen deficiency-Mitochondrial Metabolic reprogramming-microenvironment formation

Whether it is microscopic cells or macroscopic human body, energy metabolism is a necessary condition for life activities. The spleen dominates the movement, taking movement as rotation, and transforming into yin and yang. The energy conversion with the rise and fall of qi as the basic way realizes the macroscopic material transformation and information transmission. As a cell power factory, mitochondria are the main place where sugars, fats and proteins are transformed into ATP (qi) by tricarboxylic acid cycle and oxidative phosphorylation. Therefore, mitochondria are the modern biological essence of spleen, and mitochondrial energy metabolism is the microscopic embodiment of spleen dominant transport [5]. Spleen deficiency, transport loss, resulting in phlegm, turbid, blood stasis into cancer poison flow, invasion of other internal organs. Modern medicine shows that the inhibition of oxidative respiratory chain and the disturbance of energy metabolism are caused by mitochondrial damage in the process of tumor development. In order to adapt to the biological behavior of abnormal proliferation, migration,

differentiation and invasion of tumor cells, cells are reprogrammed for energy metabolism, and active glycolysis has become the main mode of metabolism. With the change of mitochondrial metabolism, the electron transmission disorder of respiratory chain leads to the imbalance of mitochondrial homeostasis and the generation of a large number of abnormal metabolites, which is closely related to the pathogenesis of "spleen deficiency and loss of health, interaction between phlegm and blood stasis, and prosperity and decline of pathogenic factors" proposed by TCM tumors [6]. At the same time, abnormal metabolism induces tumor cells to produce inflammatory chemokines, making tumor cells in chronic inflammation, which is highly consistent with the pathogenesis of inflammation-cancer transformation caused by "invisible phlegm" in TCM syndrome differentiation of spleen deficiency. Abnormal lactic acid accumulates in the interstitial space and induces cells to secrete vascular endothelial growth factor (VEGF) and transforming growth factor- β (TGF- β), which can synthesize and deposit extracellular matrix (ECM) and produce various collagen and adhesion proteins, mediate ECM remodeling, resulting in abnormal intercellular fluid flow resulting in a sharp increase of interstitial hydraulic (IFP) in tumor tissue [7]. "the husband's phlegm, the synonym of body fluid", the deposition of abnormal components in the intercellular space of tumor cells and its state of high pressure are similar to the pathological state of abnormal metabolism of spleen deficiency body fluid in TCM syndrome differentiation, dampness and turbid endogenesis, alienation and accumulation of "invisible phlegm". Pathological changes such as mitochondrial swelling and cristal membrane injury can produce a large amount of reactive oxygen species (ROS), which can up-regulate angiogenesis and promote tumor proliferation [8]. However, the disordered structure, tortuous shape and uneven thickness of neovascularization make the blood supply disorder or even leakage, and the blood is easy to become hypercoagulable state. This is related to the view of TCM that deficiency of spleen and lack of biochemical sources of qi and blood lead to non-filling of vessels; or even deficiency of spleen, imbalance of movement and transformation, accumulation of phlegm, turbidity and blood stasis lead to vascular obstruction. The pathogenesis of blood stasis and carcinogenic toxin forcing vascular hyperplasia over a long period of time is similar. Therefore, the phenotype of angiogenesis caused by the change of metabolic pattern is consistent with the pathogenesis of spleen deficiency-adverse pulse in TCM [9]. Through the method of image comparison, the spleen is associated with mitochondria, and the tumor microenvironment with low pH, chronic inflammation, high interstitial hydraulic pressure, hypoxia and lack of nutrition is formed by metabolic reprogramming based on glycolysis. The essence of TCM syndrome differentiation is the accumulation of phlegm, turbid, blood stasis and other pathological products caused by spleen deficiency.

Spleen deficiency-immune cell failure-immune escape

Normal splenic function can transform qi into blood and nourish upright qi, so it is said that "the Normal splenic function is not affected by evil". The growth of immune organs, immune cells and immune molecules all depend on

the nourishment of blood, strong temper, transfer of water grain essence to the heart, whether it is the vital qi of TCM or the immune system of modern medicine are closely related to the function of spleen. Modern medicine shows that the spleen of TCM and the lymphatic reticulo-endothelial system of human body have the same immunological connotation. Animal experiments showed that the ultrastructure of immune organs of spleen and thymus in mice with spleen deficiency syndrome was destroyed [10]. Under the influence of the development of modern medicine, immunosuppression as the main feature of tumor microenvironment is similar to the pathogenesis of TCM syndrome differentiation of deficiency of vital qi and rampant cancer toxin. The essence of immunosuppression and immune escape is that deficiency of vital qi is entangled with poison and evil glue or even unable to fight, resulting in immune imbalance, that is, uncontrollable chronic inflammatory stimulation. Based on the influence of the "seed-soil" theory, tumor cells use the warm "soil" of chronic inflammation not only support their own growth by metabolic reprogramming (warburg effect), but also weaken the function of immune cells. The change of metabolic pattern leads to the consumption exceeding the production capacity, and the tumor microenvironment is in a state of lack of nutrition, hypoxia and acidosis. Immune cells adapt to the deteriorating tumor microenvironment at the cost of changing metabolism in order to maintain their own morphology, and only T cells with sufficient activation efficiency can migrate from lymph nodes or spleen to the infected site. In the process of immune response stimulated by antigen, the demand for ATP and metabolic resources of T cells increases exponentially. However, T cells' demands for ATP and metabolic resources increase exponentially in the process of immune response to antigen stimulation. Therefore, there is a relationship of metabolic interaction and nutritional competition between tumor cells and T cells in the microenvironment. However, the fast-growing cancer cells are addicted to glucose and the increase in glycolysis rate consumes nutrients in the microenvironment. restricted metabolism leads to low T cell responsiveness and prevents immune cells from producing enough interferon- γ (IFN- γ) to induce pro-inflammatory and anti-tumor properties of CD8⁺ T cells. in order to maintain the self-immune function in the environment of low nutritional supply, T cells differentiate into pro-tumor regulatory T cell (T-reg) cells which are independent of glucose uptake and glycolysis. Hypoxia up-regulates the expression of hypoxia-inducible factor-1 α (HIF-1 α) and promotes the accumulation of reactive oxygen species (ROS) around cells, which can enhance ROS-mediated T cell inhibition. Immuno-suppression caused by insufficient energy supply can prolong the persistent state of chronic inflammation in the microenvironment, while CD8⁺ T cells fail due to long-term chronic inflammatory stimulation [11]. In addition, the tumor acidic environment, as a "protective armor", through which cancer cells can eliminate and neutralize the activity of all anti-tumor immune effectors, and transform regulatory immune cells into pro-tumor cells, which is consistent with the hypothesis of chronic inflammation caused by spleen deficiency. The change of metabolic mode not only promotes the malignant phenotype of tumor and weakens the immune response, but also the

microenvironment reacts to sculpture immune cells, forming an immune escape area characterized by immunosuppression, which is the so-called "the place of deficiency is the place of tolerance of evil". Cancer toxin is easy to reproduce and evolve in places where vital qi is weak, which is consistent with the situation that immune escape and tumor proliferation and deterioration are easy to occur in the tumor immune microenvironment. The complete Book of Jingyue records that "most people with deficiency of spleen and kidney and weakness and imbalance have the disease of accumulation." Therefore, the TCM pathogenesis of immune dysfunction is spleen deficiency.

Spleen deficiency-endoplasmic reticulum stress-tumor progression

The strong temper spreads the essence in the viscera and body of the whole body, so the function of "dispelling spleen and dispersing essence" is the main physiological link in which the spleen participates in the material metabolism of the human body. As the largest intracellular membrane system, endoplasmic reticulum (ER) is not only the core organelle of metabolic activity, but also the main place of metabolism. As a protein quality control device, endoplasmic reticulum is responsible for the biosynthesis, folding, maturation, stability and transport of transmembrane and secretory proteins. The normal function of endoplasmic reticulum promotes the glycosylation modification of synthetic proteins to make them bioactive in order to maintain protein homeostasis and normal cell life activities [12]. Therefore, the endoplasmic reticulum is very sensitive to the imbalance of cell homeostasis. Endoplasmic reticulum folding ability is impaired due to various pathophysiological injuries, resulting in the accumulation of unfolded or misfolded proteins in organelles, which induces endoplasmic reticulum stress (ERS) and induces protein chaperone (Bip) to release from the pressure sensor to activate endoplasmic reticulum unfolded protein response (UPR) [13]. Thus, endoplasmic reticulum-related degradation of (ERAD) is activated and unfolded, misfolded or unassembled proteins are cleared by cytoplasmic ubiquitin-proteasome system (Ups), so that cells can maintain the homeostasis of proteins and their life activities under internal and external pressure, but persistent endoplasmic reticulum stress exceeds its self-regulating threshold, resulting in cell imbalance. Due to the rapid growth of tumor, endoplasmic reticulum (ER) is under the high pressure of protein synthesis and secretion disorder, microenvironment hypoxia, acidosis and nutrition deficiency, and the endoplasmic reticulum stress induced by this stress is out of regulation. Activated UPR is closely related to tumor development, tumor microenvironment reconstruction, angio-genesis, invasiveness, immune-suppression and tumor drug resistance. Continuous activation of UPR in the late stage of malignant tumor progression can trigger tumor adaptation to external and internal injury, so that the tumor can not only resist endoplasmic reticulum stress-mediated apoptosis, but also survive by promoting epithelial-to-mesenchymal transformation of (EMT) and angiogenesis. At the same time, the high expression of Bip is closely related to tumor growth, invasion and metastasis, suggesting that the up-regulation of tumor Bip induced by

ER stress can promote the microenvironment adaptability and tolerance of tumor cells. XBP1, the downstream effector of inositol demand enzyme 1 (IRE1), one of the endoplasmic reticulum stress sensors, combines with hypoxia inducible factor (HIF-1 α) to activate angiogenesis and glucose metabolism to promote tumor growth and recurrence [14]. Therefore, the steady-state imbalance of endoplasmic reticulum is consistent with the pathogenesis of fine matter caused by spleen deficiency without dispersing essence. In addition, as the regulatory messenger of cell signal, Ca²⁺ plays an important role in maintaining the transmission of biological information between cells, while the endoplasmic reticulum as the storage site of Ca²⁺, excessive endoplasmic reticulum stress leads to the imbalance of Ca²⁺ homeostasis and further leads to the disorder of intercellular information transmission. The theory of the rise and fall of qi in TCM emphasizes that the rise and fall of qi is the basic form of material and energy transformation. Information theory holds that the exchange of information among cells, organs and systems must be realized with matter or energy as the carrier. The process of transfusion of qi, blood and body fluid, which takes the rise and fall of qi as the main form, realizes the relationship between various viscera, so the disorder of life activity with endoplasmic reticulum stress as the main mechanism is still spleen deficiency in TCM syndrome differentiation.

Spleen depression-chronic inflammatory stimulation-tumor and depression

Tumor-related depression refers to severe mental disorders or chronic disease syndrome affected by the diagnosis, treatment and complications of malignant tumors. Its manifestations are as follows: decreased pleasure, irritability, psychomotor retardation, fatigue, anorexia, insomnia, increased pain sensitivity and so on. TCM differentiation of disease and depression, the clinical syndrome is especially based on the spleen, spleen storage meaning, in the mind for thinking, spleen sad and sad, in the depression of the spleen does not extend, so it is depression. Under the influence of the whole concept of "unity of form and spirit" in traditional medicine, the theory of pathogenesis of emotion and the transformation of modern medical model, emotional depression and tumorigenesis are cause and affect each other. Poor mood, obstruction of qi, phlegm and qi knots lead to depression syndrome. at the same time, mental and psychological disorders can affect the occurrence and development of tumors and the quality of life of patients. First, mental depression, consumption of temper, aggravate positive deficiency, second, mental depression, Zang-fu qi stagnation, leading to the formation of pathological products such as qi stagnation, blood stasis, phlegm and turbid phlegm, contributing to the formation of tumors [15]. Modern medical research points out that the occurrence of depression caused by emotional hypertension is closely related to long-term oxidative stress and chronic inflammation, and the secretion of pro-inflammatory cytokines mediates the co-occurrence of depression and tumor. The continuous secretion of tumor necrosis factor α (TNF- α) affects tryptophan metabolism directly or indirectly by up-regulating the activity of indoleamine 2-3 dioxygenase (IDO). First, activated IDO weakens the

process of converting tryptophan to serotonin in the brain, resulting in a decrease in the concentration of monoamine transmitters and aggravating depression; at the same time, overexpressed IDO reduces host immune cell reactivity by promoting T cell differentiation to regulatory phenotype, inducing CD8⁺ T cell cycle arrest and failure, and blocking the differentiation of helper Th17. Second, IDO activates the canine uric acid (KYN) pathway, which converts tryptophan to canine uric acid (UPR), resulting in serotonin deficiency. The accumulated UPR not only inhibits the activity of CD8⁺ T and natural killer cells (NK) and tends to T-reg differentiation, but also can be further transformed into quinolinic acid (Quin), quinolinic acid as a catabolite to induce further production of inflammatory cytokines and enhance oxidative and nitrosation stress (O&NS), leading to lipid peroxidation, mitochondrial dysfunction and DNA damage. With the persistence of O&NS state, high levels of reactive oxygen species (ROS) and reactive nitrogen (RNS) further aggravate genomic instability, which are closely related to tumor cell proliferation, angiogenesis and metastasis [18]. Therefore, it has been confirmed that the activation of canine uric acid pathway mediated by chronic inflammatory stimulation caused by emotional depression is the key bridge between depression and malignant tumor. Therefore, depression and other negative emotions through the neuro-endocrine-immune axis produced by a non-specific stress response can lead to the weakening of tumor immune surveillance function, thus preventing tumor cells from killing and immune escape. This is consistent with the theory that the accumulation of pathological products such as qi stagnation, blood stasis, phlegm and turbid phlegm caused by abnormal operation of qi and blood and dysfunction of viscera caused by poor emotion in macro syndrome differentiation of TCM is consistent with the theory that it finally turns into tumor.

SUMMARY AND PROSPECT

The hidden relationship between the relevant physical and chemical indexes in SVMT is explored by the thinking method of systematic scientific analysis, and with the help of the modern scientific understanding of the macroscopic life process of the spleen visceral image, in order to achieve a new level of scientific understanding of the deep mechanism and law of spleen visceral image changes, but also increases the clear thinking of fuzzy macro understanding under the guidance of scientific theory. Based on the systematic relationship between spleen and malignant tumor, this paper expounds the scientific connotation of spleen and malignant tumor from the point of view of mitochondrial energy metabolism reprogramming, immune cell failure, endoplasmic reticulum stress and chronic inflammatory stimulation. The modern medical essence associated with malignant tumor under the condition of disorder of spleen visceral image mechanism was discussed from the subcellular level, which injected new vitality into the traditional spleen visceral image theory to guide the treatment of malignant tumor. However, the formation and perfection of the theory must be sublimated in the process of self-sublation, and the short-term understanding is not equal to the permanent truth. We believe that under the guidance of the system theory, the developing scientific theory will reveal more scientific essence of the traditional theory. It also opens up a wider

train of thought for the spleen viscera theory to guide the diagnosis and treatment of malignant tumors.

ACKNOWLEDGMENT

This work is supported by the Scientific Research Project of Key Areas of Traditional Chinese Medicine of Tianjin Health and Family Planning Commission of China (No. 2017003), the Major Project of Science and Technology of Prevention and Control of Chronic Diseases of Tianjin Science and Technology Commission (No. 17ZXMSFY00190), and the Selection and Training Project of High-Level Talents in Tianjin Health and Family Planning Industry.

Competing interests: The authors declare that they have no conflict of interest.

Citation: Zuo JH, Chang J, Zhong M, Wang XR, Xie HX, Liao DY, et al. Explain the relationship between the theory of spleen viscera and the pathogenesis of malignant tumors from the perspective of system theory. *TMR Cancer*. 2021;4(3):12. doi: 10.53388/TMRC201800103.

Executive editor: Shan-Shan Lin.

Submitted: 21 June 2021, **Accepted:** 25 June 2021, **Online:** 28 June 2021

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