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Discussion on reprogramming of tumor energy metabolism and intervention of traditional Chinese medicine based on the theory of “collateral Qi stagnation”

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Author contributions
Yi Li conceived and disigned the manuscript. Gui-Jie Wang and Chuan-Long Zhang draw the figure. Yi Li wrote the original draft. Bo Pang reviewed the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
TCM, traditional Chinese medicine; mtDNA, mitochondrial DNA; SDH, succinate dehydrogenase; IDH, isocitrate dehydrogenase; FH, fumarate hydrase.

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Abstract
The theory of stagnation of collateral Qi (Chinese medicine refers to the most fundamental and subtle substances thatconstitute the human body and maintain life activities, and also has the meaning of physiological functions) originates from the theory of collateral disease, which refers to the deficiency of Qi in the body’s collaterals, the loss of Qi and blood, and the failure of stagnation of collateral Qi, which leads to the loss of Qi, blood and body fluid, and the formation of pathological products such as deficiency, depression, phlegm, blood stasis in the local area, and ultimately damage the pathological process of collaterals. Based on the in-depth study of the pathogenesis of collateral Qi stagnation and the previous study of meridian channels, we believe that the key pathogenesis of the formation, evolution and spread of malignant tumors is “collateral Qi deficiency stagnation, collateral Qi stagnation and collateral Qi decay”. As an important energy resonance channel of the body, meridians play a key role in the process of material transformation and energy metabolism. It is believed that the small focus caused by the pathogenesis of stagnation is the cause of malignant transformation of tumor, the reprogramming of energy metabolism induced by the lesion of collateral Qi is the basis of the progress of tumor pathogenesis, and the formation of tumor microenvironment regulated by the tumor toxin vena is the root of alienation of tumor development. Guided by this theory, focusing on the correlation between collateral Qi and tumor energy metabolism, using Professor Hua Baojin's treatment method of “Regulating Qi and detoxifying” to prescribe drugs can adjust collateral Qi function, achieve the relative balance of internal environment, and then inhibit the progress of tumor. Based on the above understanding, this study tries to enlighten new diagnosis and treatment ideas under the guidance of “stagnation of collateral Qi” in traditional Chinese medicine, in order to provide some theoretical support for the intervention of traditional Chinese medicine in the process of tumor development.

Keywords: stagnation of collaterals; tumour; energy metabolism reprogramming; tumor microenvironment; integrated traditional Chinese and Western Medicine

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Background

Malignant tumors are an important cause of death in the world. Relevant statistical results show that tumor-related diseases have surpassed traditional cardiovascular and cerebrovascular diseases in the hierarchy of causes of death in many countries [1, 2]. The incidence and mortality of cancer, represented by gastrointestinal malignancies, are higher than the worldwide level in our country. The tumor prevention and treatment situation is still grim. Therefore, finding the core entry point for the treatment of malignant tumor has become an important issue in the basic and clinical research of malignant tumor. In recent years, the original theory of tumor pathogenesis has been increasingly enriched. Based on the original thinking of traditional Chinese medicine (TCM), scholars of TCM have explored the internal correlation of tumor pathogenesis from the macro perspective of body resistance deficiency, toxic accumulation, disorder of Qi (Chinese medicine refers to the most fundamental and subtle substances that constitute the human body and maintain life activities, and also has the meaning of physiological functions) activity and the micro perspective of tumor energy metabolism, microenvironment, immunity, etc. However, it is urgent to strengthen the integrated thinking of traditional Chinese and Western medicine in tumor pathogenesis theory. Explore the internal mechanism of tumor pathogenesis from the macroscopic and microscopic dimensions. Based on the choroid theory and previous research basis, this paper elaborated the biological pathogenesis of tumor from the perspective of integrated traditional Chinese and Western medicine, and explored the TCM pathogenesis theory of malignant tumor under the guidance of "collateral-Qi stagnation" theory, in order to provide ideas and basis for TCM prevention and treatment of malignant tumor [3, 4]. This article makes up for the shortcomings of previous research and the framework structure of this paper is shown in Figure 1.

Source and meaning of Qi stagnation in collaterals

The theory of collateral-Qi originated from the ancient book of Chinese medicine *Yellow Emperor's Inner Classic* (unknow author, 221 B.C.E–220 C.E.). The ancient book of Chinese medicine *Suwen · Tongpi ng Xushi Lun* (unknow author, 221 B.C.E.–220 C.E.) says: "If collateral-Qi is insufficient and there is surplus of Qi, the pulse mouth is hot and the Chi is cold." In addition, there are related descriptions of meridians and collaterals, such as *Lingshu · Xieqi Zangfu Bingxing* (unknow author, 221 B.C.E.–220 C.E.), which says: "The meridians intersect, such as ring without end." "*Lingshu · Meridians*" (unknow author, 221 B.C.E.–220 C.E.) said: "The floating and common veins, all the collaterals are also." It can be seen that the book *Yellow Emperor's Inner Classic* has made the initial conceptual discussion and explanation of the concepts of collaterals and collateralized Qi. Later on, Tian-Shi Ye (1666-1745 C.E.), a physician in the Qing Dynasty (1636–1912 C.E.), put forward the idea of "chronic disease entering collaterals", "chronic pain entering collaterals" and "chronic disease blood stasis" innovatively based on the theory of complexation, which greatly enriched the academic experience of TCM in guiding the treatment of chronic collaterals. In the new historical period of academic development, academician Wang combined with *Renzhai Zhizhi Fang* (Shi-Ying Yang, 1264C.E.) said: "The deficiency of time, expansion and reduction, deficiency Qi stay stagnant, according to the method should be warm medicine to soothe" [5]. Academician Wu put forward the theory of "deficiency Qi retention stagnation"[6,7]. Based on the research of "deficiency Qi retention stagnation" and combined with the research of philosophical Qi, medical Qi and Qi function, he put forward the theory of "Qi colli-tion", which believed that Qi colli-tion constituted the functional system of life movement. By integrating the theory of complexation with it, he proposed the theory of "deficiency Qi retention stagnation" of complexation, namely the concept of "colli-Qi stagnation". Collateralized Qi is the pulse Qi that runs through the Qi collaterals. It often moves in the same direction as the blood that runs through the blood collaterals. It plays an important role in the material transformation and energy metabolism of the human body.

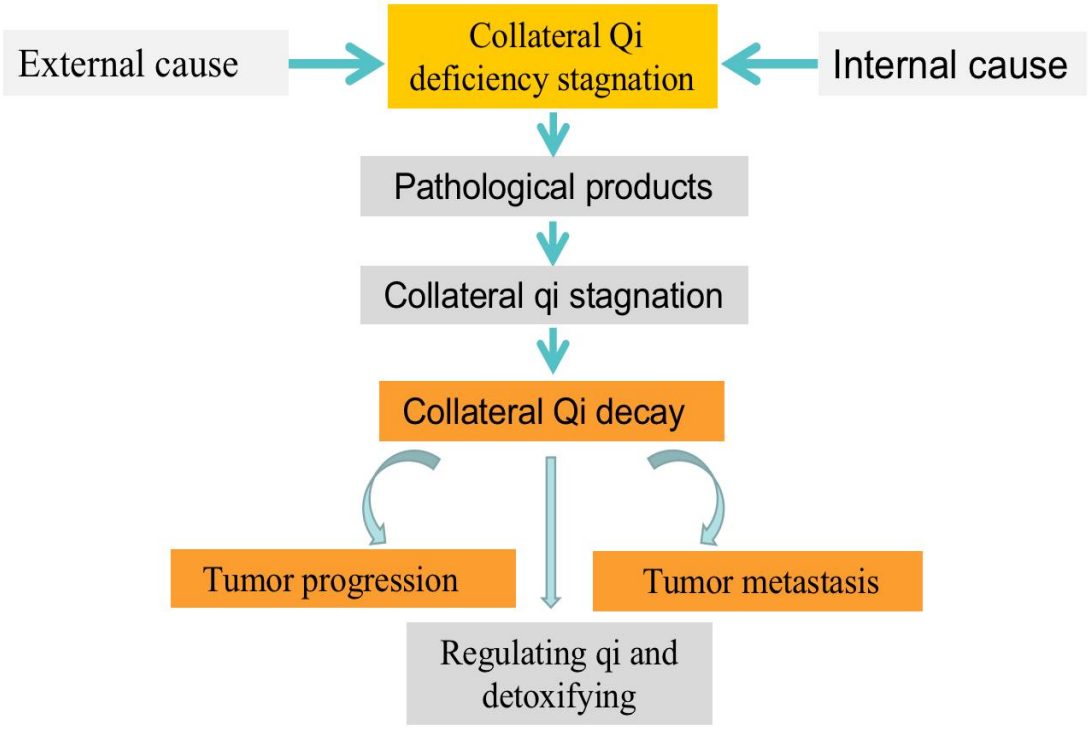


Figure 1 Article framework structure

Dynamic genetic understanding of the pathogenesis of collateral-Qi stagnation in malignant tumors

Deficiency leads to poison, phlegm stasis turns into poison, and chronic stagnation leads to poison

Lingshu · Meridians said: "Meridians, so determined to die, all diseases in, adjust the deficiency and the solid, can not be blocked". The ancient book of Chinese medicine *Yangyi Daquan* (Shi-Cheng Gu, 1760) says: "Therefore, accumulation is accumulation, which originates from people with Qi and blood deficiency (the name of the TCM disease). Therefore, it is said that strong people do not have accumulation, but weak people have it." Due to external sensation, internal injury and other factors affecting the patency of collateral channels, it will induce the formation of local deficiency, phlegm and blood stasis micro-environment, evil spirits are kept for a long time, and evil spirits remain in the deficiency area. Moreover, chronic illness and injury often hinder the distribution of collateralized Qi, resulting in functional dysfunction of the operation of Qi, blood and body fluid. The rise and fall of Qi is out of harmony, and it is called "collateralized Qi stagnation". Some studies believe that the variation of collateralized Qi is the early stage of transforming from functional lesions to organic lesions, which is also the direct factor of transforming pathological products such as phlegm and blood stasis into cancer toxicity. Carcinogenic evil represented by "dampness poison, phlegm poison, stagnation poison, fire poison, blood stasis poison" can further block in the complex, stop accumulation, stagnation aggravates secondary damage to the complex, stagnation for a long time can damage the Spleen and Stomach (refers to the Spleen and Stomach channels. According to TCM, the five elements of the spleen and stomach belong to the earth and belong to the middle coke. They jointly shoulder the heavy responsibility of generating Qi and blood, which is the foundation of acquired nature), Qi and blood biochemical deficiency source, forming a vicious cycle of carcinogenic evil gas and human body positive Qi mutual damage. In addition, the abnormal metabolic function caused by collagal-Qi stagnation is often consistent with the special energy metabolism characteristics of tumor energy metabolism reprogramming phenomenon, Qi and blood stagnation for a long time can not run, and can also become toxic and lead to deficiency. On the basis of the formation of complex evil, the concurrent transformation of "deficiency-phlegm stasis-stagnation-toxicity" will accumulate cancerous tumors over time.

Collateral-Qi stagnation and tumor angiogenesis

Blood vessel is the important basic structure of human circulation and the key interface between circulation and different organ environments. It plays a key role in body tissue homeostasis and responding to disease challenges. Vascular control of the tissue microenvironment is essential in development, hemostasis, inflammation and metabolism, as well as in cancer and metastasis. Studies have found that tumor growth is closely related to the formation of new blood vessels, because tumor growth requires a large amount of nutrient supply, and the formation of new blood vessels creates conditions for the uncontrolled growth of tumors. At the level of TCM, *Suwen · Six Micro Contents of Great Theory* (unknow author, 221 B.C.E.–220 C.E.) says: "Overbearing harm, bearing is control, control is biochemistry, external rise and fall, harm is chaos, biochemical serious disease". From the perspective of TCM image thinking, it is believed that the choroid and tumor blood vessels are similar in macroscopic structure, and the deficiency of collateral-Qi mediated by collateral-Qi deficiency choroid blood stasis is an important material basis for tumor angiogenesis [8]. In the human body, the complex has the function of spreading the Qi and blood running in the meridians all over the body. It is a network structure with precise structure, wide range of operation, providing material exchange, managing energy metabolism, and belonging to the functions of limbs and bones. As a special pathway and energy resonant channel of the body, the complexions can induce and retain evil spirits and interact with evil spirits. If evil spirits are strong, the hyperactivity of the collars and channels and the loss of the network can induce the continuous growth of tumor blood vessels and promote the metastasis of tumor bodies.

Reprogramming biological characteristics of tumor energy metabolism

Most modern studies believe that tumor is a kind of energy metabolic disease, and its abnormal energy metabolism pattern is an important basis for tumor formation, evolution and metastasis. By analyzing the understanding of modern medical scientific research on inflammation and tumor, it is concluded that the damage of mitochondrial energy metabolism, the up-regulation of aerobic glycolysis metabolism and the malignant transformation of microenvironment are the important preconditions leading to the imbalance of energy metabolism and thus carcinogenesis. In the process of ontogeny, all life activities carried out in the body are inseparable from the energy supply in the process of substance transformation. In the normal body without cancer, most energy output comes from the oxidative phosphorylation of mitochondria (accounting for about 90% of energy supply), and ATP generation through glycolysis only accounts for 10% of the total supply. However, in the reprogramming mode of energy metabolism in tumor, the energy supply structure is migrated greatly, which is mainly related to mitochondrial damage and aerobic glycolysis.

Mitochondrial DNA (mtDNA) is a double-strand closed-loop molecule with total length 16596bp, containing 2 rRNA genes, 22 tRNA genes and 13 oxidative phosphorylated polypeptide coding genes, which are unique genetic material mitochondrial DNA [9]. In the damaged energy metabolism process of mitochondria, the oxidative phosphorylation process is weakened and the percentage of production capacity is reduced. More and more studies have shown that damaged energy metabolism disorders are closely related to mtDNA damage, mitochondrial membrane potential abnormalities, and decreased metabolic key enzyme activities. In addition, mutations of key enzymes of mitochondrial metabolism also play a key role in the malignant transformation of microenvironment and thus the establishment of a carcinogenic environment. For example, the key enzymes of mitochondrial metabolism in the tricarboxylic acid cycle, such as succinate dehydrogenase (SDH), isocitrate dehydrogenase (IDH) and fumarate hydrase (FH), etc. have been confirmed to have mutations in tumor cells.

In addition, as far as tumor cells are concerned, the excitation of energy metabolism of aerobic glycolysis is the precise selection of metabolic mode change in tumor during the transformation stage of inflammatory cancer. This energy metabolism pattern with high glucose uptake rate but extremely low productivity efficiency plays a key role in the late evolution and metastasis of tumor cells.

Medical records

Patient, female, 72 years old. First visit on January 9, 2021. Chief complaint: Ovarian cancer 3 months after surgery, last chemotherapy 2 months. The patient visited a local hospital in October 2020 due to "abdominal pain for 2 months". The patient was diagnosed as ovarian serous cystadenocarcinoma (stage IV), and underwent "total hysterectomy, double adjunctive resection and intraperitoneal perfusion chemotherapy". During the operation, uterine atrophy was observed, uterine surface inflammation and bleeding, the posterior wall of the uterus and the rectum were dense adhesion, the uterine rectal fossa was closed in the shape of frozen pelvis, and the right ovarium was hard and adhered to the right pelvic wall with the right fallopian tube. Postoperative pathological diagnosis revealed serous papillary adenocarcinoma in both ovaries, carcinoma in the left fallopian tube, carcinoma in the serous surface of the uterus, and carcinoma in the serious surface of the cervix. Intraperitoneal infusion of 30mg lobaplatin was performed on October 19, 2020 (6 days after surgery), intravenous administration of 210mg paclitaxel was performed on October 20, and the chemotherapy regimen of 20mg lobaplatin was completed on October 21. After chemotherapy, the

symptoms of fatigue and poor tolerance were obvious, and postoperative adjuvant chemotherapy was not performed. Symptoms are as follows: poor intake, poor sleep, even worse fatigue, noisy discomfort in the heart, pain in the right abdomen, swelling of the back of the feet in the morning, dark spots on the face, obvious forehead around the eyes. The tongue is light and dark, the moss is thin and white and dry, the pulse string is fine, and the Chi Pulse (Part of the two tiny pulses.) is heavy and weak. Western Medicine diagnosis: ovarian serous cystadenocarcinoma (stage IV); TCM diagnosis: disease, syndrome is collateral-Qi deficiency, phlegm-stasis interjunction. Treatment: To strengthen the body resistance and promote collaterals, regulating Qi and detoxifying. Prescription: Dangshen (*Codonopsis Radix*) 10g, Taizishen (*Pseudostellariae Radix*) 20g, Zhihuangqi (*Astragali Radix Praeparata Cum Melle*) 20g, Chishao (*Paeoniaeradix Rubra*) 10g, Mudanpi (*Moutan Cortex*) 12g, Jiegeng (*Platycodonis Radix*) 12g, Xingren (*Armeniacae Semen Amarum*) 12g, Chaobaibiandou (*Lablab Semen Album*) 12g, Shanyao (*Dioscotea Rhizoma*) 20g, Baizhu (*Atractylodis Macrocephale Rhizoma*) 15g, Jineijin (*Galli Gigerii Endothelium Corneum*) 20g, Fuling (*Poria*) 30g, Dongguapi (*Benincasae Exocarpium*) 30g, Lianzixin (*Nelumbinis Plumula*) 2g, Lianzi (*Nelumbinis Semen*) 12g, Jixingzi (*Impatientis Semen*) 10g, Shijianchuan *(Herba Salviae Chinensis*) 15g, Banzhilian (*Scutellaria Barbata Herba*) 15g, Taoren (*Persica Semen*) 10g, Gouqizi (*Lycii Fructus*) 15g. A total of 14 doses, 1 dose a day, decocted in water, morning and evening. On January 23, 2021, the second diagnosis: the patient's poor appetite, insomnia improved, abdominal pain and noise disappeared, fatigue slightly reduced but still felt very tired, and the remaining symptoms were the same as before. The decoction method is the same as before. The dosage of Huangqi (*Astragali Radix*) and *Dioscotea Rhizoma* are increased to 30g. 14 doses are given and the decocting method was the same as before. On February 6, 2021, the third diagnosis: the patient's fatigue was improved, the swelling of the back of the foot was significantly improved, the dark spots on the face did not disappear, but the dull feeling of the face was significantly reduced, and the face began to show luster. The top of the *Benincasae Exocarpium*, *Nelumbinis Semen*, *Persica Semen*, *Herba Salviae Chinensis* are increased to 30g, in addition to the Baihuasheshecao (*Hedyotis Herba*) 30g, Tufuling (*Smilacis Glabrae Rhizoma*) 15g. 14 doses were administered, and the decocting method was the same as before. On February 20, 2021, the fourth diagnosis: The patient's fatigue was significantly improved, and his tongue and pulse were improved. If the effect is not more prescription, the defense prescription is as before. After converting the amount of medicine, decoction is converted to pilula.

Evaluation: the patient's Yuan Qi (it is produced by the essence of the parents, and the combination of the acquired Shuigu Qi and the natural QingQi results in Yin Qi and Yang Qi) is deficient after the whole uterus and double adnexectomy are excised, abdominal cavity perfusion chemotherapy damage to the Qi of collaterals, so the patient looked tired when seeing a doctor, the damage of collaterals Qi is poor ingestion, Yin that does not collect Yang (Yin-yang theory holds that the world is a material whole, and everything in the universe not only has the unity of opposites of yin-yang, but also its occurrence, development and change are the result of the unity of opposites of Yin-yang and Qi) leads to poor sleep, the heart noise is collaterals Qi deficiency and slightly heat disturb the mind, abdominal pain is postoperative blood stasis, swelling of the back of the foot and facial dark spots are local signs of abnormal water metabolism. The pathogenesis of this disease is complex, if the treatment is not timely, it is easy to delay the course of the disease, taking into account the patient's body hormone deficiency, not resistant to attack, so the disease differentiation stage diagnosis and treatment thinking, the first to help the healthy Qi, then attack the evil, medication in accordance with the method of small agent slow, grasp the main syndrome flexibly adjust the amount of fuzheng and detoxification drugs. At the first diagnosis, combined with the patient's symptoms, on the basis of regulating Qi and supplementing the deficiency of collars, *Nelumbinis Plumula*, *Poria* and *Benincasae Exocarpium* were added to soothe the spirit and relieve the swelling. At the second diagnosis, the patient's fatigue was not significantly reduced, so increased the amount of *Astragali Radix* and *Dioscoreae Rhizoma* to tonify Qi and spleen. Fatigue improved significantly during the three diagnosis, indicating that the patient's healthy Qi had gradually recovered. Therefore, based on the method of regulating Qi and detoxifying, the amount of the original anti-cancer and detoxifying drugs was increased. At the late course of the disease, pills are given after treatment, pills with slow, water dripping through the stone, can slow together strengthening body resistance and detoxification method. Two good deeds lead to merit.

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