Metabolic theory of ovarian cancer and the potential of traditional Chinese medicine treatment: A hypothetical framework

Hao-Chen Yuan1, Xin-Ke Wang2, Rui-Jia Xu3, Hui-Jie Li*4

1College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250355, China. 2Medical College, Shandong University of Traditional Chinese Medicine, Jinan 250355, China. 3College of Acupuncture-Moxibustion and Tuina, Shandong University of Traditional Chinese Medicine, Jinan 250355, China. 4Department of Oncology, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan 250013, China.

*Corresponding to: Hui-Jie Li, Department of Oncology, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, No.16369 Jingshi Road, Jinan 250013, China. E-mail: 2008lihuijie@163.com.

Abstract
Ovarian cancer (OC) is one of the most common malignant tumors in the female reproductive system. Its mortality is the highest among gynecological malignant tumors. Its metabolic characteristics play an essential role in the occurrence and development of diseases. Traditional Chinese medicine (TCM) can assist Western medicine and enhance the curative effect in treating OC. Studying its application and intervention on metabolic targets is highly clinical significance. Based on this, this paper reviews the glucose metabolism, lipid metabolism, and amino acid metabolism of OC in order to explore the metabolic characteristics of OC. Moreover, the status of TCM in treating OC based on metabolism is reviewed from the aspects of TCM monomer, TCM compound, and TCM external treatment to provide ideas and basis for treating OC with TCM.

Keywords: ovarian cancer; metabolism; traditional Chinese medicine; hypothetical framework

Author contributions
Hao-Chen Yuan designed and wrote the manuscript. Xin-Ke Wang and Rui-Jia Xu were responsible for collecting the literature. Hui-Jie Li was involved in the conception and revision of the manuscript. The authors have read and approved the final version.

Competing interests
The authors declare no conflicts of interest.

Acknowledgements
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Abbreviations
TCM, traditional Chinese medicine; OC, Ovarian cancer; DC, dendritic cells; LPS, lipopolysaccharides; RT-qPCR, real-time fluorescence quantitative polymerase chain reaction; HK2, hexokinase-2; HK2, hexokinase-2; FASN, Fatty Acid Synthase Gene; SCD1, Stearoyl-CoA desaturase 1; FIGO, Federation International Association of Gynecology and Obstetrics; MDM2, murine double minute 2; DHM, dihydromyricetin.

Peer review information
Medical Theory and Hypothesis thanks all anonymous reviewers for their contribution to the peer review of this paper.

Citation

Received: 19 July 2023; Accepted: 28 July 2023;
Available online: 25 August 2023
© 2023 By Author(s). Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license. (https://creativecommons.org/licenses/by/4.0/)
Background

Ovarian cancer (OC) is a common gynecological malignant tumor; its morbidity and mortality are among the highest in female reproductive system malignant tumors. The Globocan Database predicts that by 2040, compared with 2020, the number of new cases of OC in China will increase by 17.9%, and the number of deaths will increase by 33% [1]. In recent years, as important factors affecting the occurrence and development of OC, abnormalities in energy and mitochondrial metabolism have gradually become a research hotspot. In-depth exploration of the pathogenesis of OC and seeking effective treatment for metabolic pathology have become urgent problems in the field of OC research. In this paper, the correlation between glucose metabolism, lipid metabolism, amino acid metabolism and the pathogenesis of OC is expounded, and the metabolic mechanism of traditional Chinese medicine (TCM) monomer, TCM compound, and external treatment of TCM in the treatment of OC is reviewed, in order to provide ideas for clinical research and treatment of OC.

Prominent features of OC metabolism

The metabolic mechanism of OC is very complex. Studies have shown that the occurrence and development of OC are closely related to energy metabolism. The three major energy metabolisms are glucose metabolism, fat metabolism and protein metabolism, which are important energy supply pathways and pathological links for tumor growth. The core of energy metabolism is to produce intracellular energy supply substances through oxidative phosphorylation and substrate phosphorylation [2]. OC is a high-incidence tumor in women. Its energy metabolism is unique and plays an important pathogenic role in the occurrence and development of tumors. Studying the energy metabolism mechanism and characteristics of OC exploring the relationship between glucose metabolism, lipid metabolism and amino acid metabolism, has an important impact on the treatment of OC from the perspective of metabolism.

The characteristics of glucose metabolism, lipid metabolism and amino acid metabolism in OC

Characteristics of glucose metabolism in OC

Glucose metabolism is one of the main types of energy metabolism and is considered to be the main way of tumor energy metabolism. In the early 1920s, biochemist Otto Warburg revealed the aerobic glycolysis of tumors [3]. Tumor cells take glycolysis as the main production mode in both aerobic and anaerobic environments. This atypical glucose metabolism phenomenon is called the Warburg effect or “aerobic glycolysis”, which can provide energy for tumor cell proliferation.

With the progress of glycolysis in tumor cells, glucose metabolism, lipid metabolism and protein metabolism of tumor cells are affected to a certain extent, anabolic and pentose phosphate pathways are up-regulated, immune cell metabolism is reprogrammed, effects like weakening inflammatory response and promoting cancer appear, such as the transformation of macrophages from M1-like to M2-like during tumor development, which is conducive to tumor growth [4]. When dendritic cells (DC) come into contact with antigen activation under normal conditions, it should be manifested as up-regulation of MHC I and MHC II molecules, CD80, CD86, and CD40 costimulatory molecules. Li et al. confirmed that lipopolysaccharides (LPS) activated DC are consistent with this performance, while DC cultured in tumor cells are inverted, which is more significant under hypoxic conditions, proving that lactic acid produced by tumor cell glycolysis can inhibit dendritic cell activation, thereby inhibiting antigen presentation, lead to tumor progression [5]. Many scholars are committed to finding substances that affect the glycolysis of OC cells to broaden the treatment of OC from a metabolic perspective. Warburg effect has been considered a special phenomenon of cancer metabolism. The high uptake of glucose by malignant tumor cells makes glucose derivatives play an important role in tumor molecular and metabolic imaging. Among them, 99Tcm-labeled glucose derivatives have shown good ability to distinguish benign and malignant lesions and to diagnose and stage malignant tumors, which have good research and clinical application prospects [6]. Ying Minli found that high expression of microRNA-29a can significantly inhibit the proliferation of OC cells and the level of glucose metabolism in cancer cells [7]. It is lowly expressed in OC tissues and OCSC2V3 and OVCA3 cells are highly expressed in adjacent normal tissues, which affects the tumor microenvironment. Li Li et al. reverse transcription real-time fluorescence quantitative polymerase chain reaction (RT-qPCR) found that mir-125B-5p reduced glycolysis of OC cells by negatively regulating hexokinase-2 (HK2) and inhibited tumor cell growth by reducing energy metabolism pathway [8].

Characteristics of lipid metabolism in OC

Abnormal lipid metabolism plays a major role in inflammatory diseases, cardiovascular metabolism, and nervous system diseases and the etiology, pathology and sequelae of various cancers, which is an important way for OC cells to meet the energy needs of continuous growth. Singh Shailendra found that, the Fatty Acid Synthase Gene (FASN) can affect the structure and function of cell membranes by passing the signal pathway of Post-Translational palmitoylation in cancer [9,10]. Further study on the characteristics and mechanism of lipid metabolism in OC is of positive significance for the development of anti-tumor drugs targeting FASN. Bai Yingjie used the immunohistochemical SP method to verify that Stearoyl-CoA desaturase 1 (SCD1) is highly expressed in epithelial OC tissues [11]. Its expression level is related to the Federation International Association of Gynecology and Obstetrics (FIGO) stage and greater omentum metastasis. It is an independent risk factor for epithelial OC and provides a new biomarker for epithelial OC.

Characteristics of amino acid metabolism in OC

Glutamine metabolism is closely related to OC. Numerous studies have shown that the metabolism, migration and invasion of OC cells depend on glutamine. Glutamine metabolism has a great influence on the malignant progression and poor prognosis of OC. In April 2021, Reinfeld Bradley I published a study in Nature using PET tracers to measure glucose and glutamine uptake by specific cell subsets in the tumor microenvironment. It was found that cells in the tumor microenvironment have a programmed nutrition distribution mechanism, in which cancer cells have the highest uptake of glutamine, glutamine metabolism inhibits the glucose uptake of cancer cells, and immune cells such as macrophages mainly uptake glucose, thus affecting the metabolic processes and activities of immune cells and cancer cells in the tumor microenvironment [12]. Prasad Parash et al. found that glutamine starvation reduced the migration and invasion properties of the OC cells, PA1 and SKOV3. Further study of the effect of glutamine metabolism on cancer pathogenesis is helpful to explore the diagnosis and treatment of OC from the perspective of etiology, which has important clinical significance [13].

The relationship between glucose metabolism, lipid metabolism and amino acid metabolism in OC

It remains debated whether systemic metabolic dysregulation alters OC progression and response to treatment. Studies have shown that metabolites and metabolic regulators promote chemoresistance, maintain the CSC population, stimulate metastasis, induce epigenetic reprogramming, and facilitate evasion from anti-tumor immunity [14]. Unique metabolic features have been described in OC cells and tumors, so further study of the relationship between different energy metabolic pathways in OC is helpful to inhibit the occurrence and development of OC from the perspective of mutual intervention of metabolic pathways, which plays an important role in proposing new treatment strategies.
Effect of OC metabolism on immunity

Numerous studies have shown that the occurrence and development of cancer are closely related to immune abnormalities. Studying the mechanism and characteristics of immune abnormalities in OC and exploring potential methods of immunotherapy are the research directions that have attracted much attention in recent years. A clinical study of Wang Beibei has shown that cellular immunotherapy can attack the overexpression of drug-resistant proteins in tumor cells, reduce their function, and enhance the effect of chemotherapy [15]. Zheng Jialiang et al. found that the murine double minute 2 (MDM2) gene was a reliable prognostic biomarker and was closely related to cancer immunity, providing a potential immunotherapeutic target for OC [16]. The study of possible targets for immunotherapy is helpful in developing drugs that inhibit cancer from the perspective of immunity and has high research value.

Effect of TCM treatment on metabolism of OC

Study on the TCM treatment of OC based on metabolic

TCM does not have the name of OC. The earliest description of ovarian tumors can be traced back to “Huangdi Neijing Lingbu” (Yellow Emperor’s Inner Classic: Spiritual Pivot; 221 B.C.E.–220 C.E.), in which it is mentioned that “Cold Qi (One of the seven gases.) is present outside the intestines, competing with Defensive Qi (It is a kind of Yang Qi.), 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) cannot flow, but due to its connections, it becomes endogenous due to addiction. Evil Qi (Evil is an etiological term. It is disease evil, generally refers to all kinds of treatment factors,) arises, and polyps arise.” Describes the pathogenesis of ovarian tumors. TCM plays an important role in the prevention, treatment and prognosis of OC. In recent years, the research on the role of TCM monomer in the treatment of OC has gradually increased, and the role of TCM compound has also been paid attention to by many scholars. Studying the tumor treatment mechanism of TCM monomer or compound from the perspective of metabolism will provide a theoretical basis for the treatment of tumors with TCM and have good development prospects.

TCM monomer

Chinese medicine monomer has an obvious curative effect in the inhibition and treatment of OC and has become a hot spot in tumor research. Jing Jing et al. used cisplatin-resistant human OC cell line A2780/DDP to study and found that gentiopicroside could inhibit the proliferation of A2780/DDP, promote apoptosis, and enhance the sensitivity of human OC cell line A2780/DDP to cisplatin [17]. The mechanism may be related to the up-regulation of p53 expression level and phosphorylation level and down-regulation of Bcl-2, XIAP and Survivin expression levels. Through the study of OC cell SKOV-3 in vitro, Xie Cheng et al. found that quinilazin could significantly inhibit the proliferation, migration and invasion of OC cell SKOV-3 and induce its apoptosis [18]. The mechanism may be related to the down-regulation of JAK2/STAT3 signaling pathway. Tan Wupeng et al. found that dihydromyricetin (DHM) may regulate macrophage polarization through the PI3K/Akt pathway and inhibit macrophage-induced SKOV3 cell proliferation and invasion [19]. The use of TCM monomer-assisted OC treatment has important research and application value.

<table>
<thead>
<tr>
<th>Active ingredients/single herb</th>
<th>Composition source or</th>
<th>Experimental model and processing</th>
<th>Related mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentiopicroside [17]</td>
<td>Rough gentian root</td>
<td>Human ovarian cancer cell line A2780/DDP was treated with cisplatin 5 mg/L and gentiopicroside 15 μmol/L for 24 h and 48 h</td>
<td>Up-regulated the expression of p53 and phosphorylation level, down-regulated the expression levels of BCL-2, Xiap and Survivin</td>
</tr>
<tr>
<td>Quinilazin [18]</td>
<td>Dry stem of Rhamnaceae plant drupes</td>
<td>Human ovarian cancer cell line SKOV-3 was treated with 0, 10, 20, 30 μmol/L for 48 h, and further treated with 30 μmol/L JAK2 inhibitor AG490 (40 μmol/L) for 24 h</td>
<td>Down-regulation of JAK2/STAT3 signaling No. pathway</td>
</tr>
<tr>
<td>Dihydrorhizoma (DMY) [19]</td>
<td>Bigedentate amelopsis twig and leaf</td>
<td>Human ovarian cancer cell line SKOV-3, RAW264.7 macrophages were treated with DMY (60 mg·L⁻¹) for 24 h, and then RAW264.7 cells and SKOV3 cells were co-cultured for 24 h</td>
<td>The mechanism of regulating tumor-associated macrophage polarization through PI3K/Akt pathway</td>
</tr>
<tr>
<td>Inratin [20]</td>
<td>Shorthorned epimedium herb</td>
<td>Human ovarian cancer cell line SKOV3, 5, 10, 20 μmol/L was treated for 48 h</td>
<td>Down-regulation of p-PI3K and p-Akt in PI3K/Akt signaling pathway White expression level</td>
</tr>
<tr>
<td>Curcumol [21]</td>
<td>Turmeric rhizome</td>
<td>Human ovarian cancer SKOV-3 cells were treated with 12.5, 25.0, 50.0, 100.0 μg/mL for 24, 48, 72 h</td>
<td>Down-regulation of p-PI3K and p-Akt in PI3K/Akt signaling pathway White expression level</td>
</tr>
<tr>
<td>Tripterine [22]</td>
<td>Common threewingnut root leaf or flower</td>
<td>Human ovarian cancer cell line HEYA8 was treated with 0.00, 0.05, 0.10, 0.20, 0.40, 0.60, 1.20 and 2.40 mg/L for 0, 12, 24, 48 and 72 h</td>
<td>Inhibition of PI3K/Akt signaling pathway</td>
</tr>
</tbody>
</table>
Resveratrol [23] Plants such as grapes, veratrum and Japanese wild weeds Human ovarian cancer cell line SKOV-3 treated with low, medium and high concentrations (1.0 × 10^4, 5.0 × 10^4, 2.50 × 10^5 mol/L) of drugs for 24, 48 h

Chinese herbal compound

The clinical research on the application of TCM compounds in cancer treatment has gradually increased, and the formula and selection of drugs under the thinking of syndrome differentiation and treatment of TCM have gradually received attention. The clinical application of TCM in the treatment of OC often pays attention to promoting blood circulation and removing blood stasis. According to different syndrome types, prescriptions are combined to play the role of Warming Yang and Resolving Qi (The method of treating Yang deficiency syndrome by combining warm Li medicine and tonic medicine.), Invigorating Spleen and Resolving Phlegm (Use tonifying qi products to promote temper, transport phlegm turpitude, and treat phlegm dampness syndrome of treatment.), Removing Pathogenic Factors (Support is to help the healthy qi, enhance the body’s disease resistance; Dispelling evil is to remove pathogenic evil and make evil go to positive safety.) and tonifying healthy energy, and adjusting patients’ autoimmune. Research shows Wenyang Huaji prescription can enhance the body’s own gasification function through the theory of “Yang transforms into Qi” (Pointing Yang to transform Qi) in TCM, which is helpful to strengthen the body resistance and eliminate pathogenic factors, warm the meridians, remove blood stasis and eliminate symptoms, and can directly or indirectly regulate energy metabolism, which is possible to treat malignant tumors such as OC [24]. Wang Dongmei et al. found that Lichong Decotion had a significant inhibitory effect on ID8 cells of ovarian epithelial carcinoma in BALB/C mice and could promote its apoptosis. The mechanism of TCM compounds in the treatment of ovarian cancer from the perspective of metabolism remains to be further studied [25].

External treatment

External treatment of TCM has the characteristics of “simple and effective”. It is widely used in the treatment of malignant tumors. The common methods of external treatment of TCM are acupuncture and patching. Acupuncture and moxibustion, including acupuncture and moxibustion, can be applied to different stages of OC treatment, alleviate the occurrence and development of complications, and promote the recovery of patients [26]. Yuan Chao conducted clinical trials to prove that Tiaoshen acupuncture can relieve fatigue symptoms during chemotherapy in patients with OC of spleen deficiency type and can improve the quality of life and mild to moderate depressive symptoms of patients [27]. Moxibustion for OC patients with extensive pelvic metastasis after the operation of peritoneal effusion can play the effect of dissipating dampness and promoting Qi, warming Yang, and dispelling cold(It refers to the treatment of Yang deficiency by warming Yang Qi and removing cold evil from the body), invigorating primordial Qi (Qi is the basis of human life, sufficient Qi can restore the function of the spleen and stomach, improve the weak condition.), promote the absorption of peritoneal effusion [28]. Acupoint application is the “transdermal drug delivery” of modern medicine, which is often used in combination with other treatments in the clinic. It can play the role of supporting healthy energy to eliminate evils, eliminating ascites, and alleviating OC with ascites from the perspective of external treatment of internal diseases of Traditional Chinese Medicine [29]. Reasonable selection of external treatment of TCM can play the role of “internal and external treatment” and enhance the clinical efficacy. At present, the research on the treatment of OC by external treatment of TCM is mainly based on clinical research, and the mechanism is not clear. This will be a new way to study the mechanism of TCM in the treatment of OC.

Conclusion

As an important cause and pathological link in the occurrence and development of OC, metabolism has high research value for optimizing treatment plans and developing new drugs, which is worthy of further study. With the increasing application of TCM in the treatment of cancer, exploring the mechanism of TCM in the treatment of OC from the perspective of metabolism is helpful to further expand its application in the treatment of cancer and provide more treatment options for the clinic to give full play to the TCM thought of “individulized treatment” and “corresponding prescription and syndrome” in the treatment of OC, and obtain better curative effect.

In the treatment of OC, TCM mainly plays the role of adjuvant chemotherapy, alleviating complications and promoting the rehabilitation of patients. More and more studies have shown that Chinese medicine monomers and compounds have a broader application space in the clinical treatment of OC. How to use TCM monomer, compound, Chinese patent medicine and external treatment of TCM to exert targeted inhibition of OC, interfere with the metabolic mechanism of tumor cells, enhance clinical efficacy, and optimize treatment plans from different stages of treatment and rehabilitation has important clinical value.

At present, there are few studies on treating cancer by TCM from the perspective of metabolism, and its mechanism and drug compatibility scheme still has a large research space, which is worthy of further exploration. The results of many clinical trials show that TCM has unique advantages in cancer treatment and can also be used as an adjuvant therapy to enhance efficacy, give full play to individual advantages, and improve the quality of life of patients. Chinese medicine monomer can regulate multiple signaling pathways of OC, such as PI3K/AKT, Wnt/b-catenin, NF-kB, Notch, etc., but it only stays at the level of cell and animal experiments [30]. The application of external treatment of TCM in alleviating patients’ pain and prolonging life still needs more experimental and clinical research to enrich cancer treatment. The mechanism of acupuncture and other external treatment methods still needs further study. An in-depth exploration of its mechanism will help to better guide clinical application and provide more theoretical support for TCM external treatment methods. In terms of prevention, the use of TCM to treat precancerous lesions has continued to receive attention and application for decades. Further exploration of its mechanism can provide ideas for cancer treatment and is expected to open up new ways of intervention.

References


8. Li L, Hou ZM. MIR-125B-5p reduces tumor energy metabolism and inhibits tumor cell proliferation by regulating hexokinase-2 in ovarian cancer tissues. *Chin J Cancer* 2021;40(9):394–403. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uq0lhG8C44YLT0AItRkibYV5v7s7i7pRms2pqw6bfRutuo1mHidxy9b7c7jw_xwvB1p1FLd90VHahwPj3Nj3IFRLOGcr5yGkuniplatform=NZKPT


15. Wang BB. The effect and clinical value of chemotherapy combined with cellular immunotherapy for recurrent ovarian cancer. Nanjing Rehabilitation Medical Association. Proceedings of the Fourth National Academic Exchange Conference on Rehabilitation and Clinical Pharmacy. 2023. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=XMRekh29YV-bwSvWD3fnnzygwzyFajaoXcavrc65S9pLxRX7Keq9GdrDXJk0H8pCqbb9n02t1lKIQkuYoB9q9l0pQhUryyLcxXbn6-oX0I8U9xobkhNISIjSm3-bdtHqyop=0&uniplatform=NZKPT&lan=CHS


