A summary of research on molecular mechanism of action of traditional Chinese medicine for aiding neoadjuvant chemotherapy for breast cancer.

Tang Binbin[1], Jiang Ying[2], Yang Hongjian[3], Zhang Xiping[3*]

[1]Second Outpatient Department of Traditional Chinese Internal Medicine, Tongde Hospital of Zhejiang Province, Hangzhou, Zhejiang Province, PR China

[2]Department of Traditional Chinese Medicine, Integrated Traditional Chinese and Western Medicine Hospital of Xihu District, Hangzhou, Zhejiang Province, PR China

[3]Department of Breast Surgery, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, PR China

Abstract

Although neoadjuvant chemotherapy is a standard therapy for treating locally advanced breast cancer, it usually can't achieve expected results owing to patients' different chemotherapeutic sensitivity. At present, some certain progress have made in treating breast cancer by adjuvant chemotherapy combined with Traditional Chinese Medicine (TCM). Being effective for suppressing tumor growth, improving immunity, enhancing efficacy and removing toxicity, TCM can improve chemotherapy effects and patients' prognosis. In this paper, the moderating roles of TCM in neoadjuvant chemotherapy for breast cancer are discussed from the perspective of molecular biology.

Introduction

Neoadjuvant chemotherapy for breast cancer has become a standard therapy for treating locally advanced breast cancer. More and more patients are benefiting from neoadjuvant chemotherapy. However, individuals are sensitive to chemotherapy to different extent, some patients don't benefit from it. What's worse, a small number of patients' diseases would be even aggravated after they are treated by neoadjuvant chemotherapy. How to predict different patients' sensitivity to chemotherapy and further improve the effects of neoadjuvant chemotherapy has become one of hot research topics at present. The good roles of Traditional Chinese Medicine (TCM) in improving neoadjuvant chemotherapy for breast cancer and patients' prognosis have been demonstrated in clinical practices, whereas its mechanism of action is still unclear. In this paper, previous research on the bidirectional regulation roles of TCM in neoadjuvant chemotherapy for breast cancer is reviewed based on biological indicators related to therapeutic effects. Besides, therapeutic effects of TCM and corresponding mechanisms are evaluated and discussed from the perspective of molecular biology.

Bidirectional Regulation of Expressions of Estrogen and Progesterone Receptors

Estrogen Receptors (ER) and Progesterone Receptors (PR) are important molecules for regulating cell growth and development in reproductive organs. They are inside the nucleus of normal mammary epithelial cells, regulating the growth and differentiation of the mammary cells. Their expression levels are important prognostic factors for breast cancer and parameters for predicting responses to hormone treatment. Patients with positive expressions are characterized by distinct differentiation of breast cancer cells, low proliferation rate, relatively slow progression of diseases and sensitivity to endocrine therapies. Hence, it is important for improving living standards and prognosis of patients with breast cancer by upregulating expression level of hormone receptors. For ER-positive or PR-positive patients, tumors can be removed to treat breast cancer by inhibiting estrogen synthesis, decreasing level of estrogen, blocking combination of estrogen with ER, partially or fully inhibiting activity of ER and suppressing the growth of estrogen dependent breast cancer cells. Over the past few years, the research has confirmed that patients whose expression level of hormone receptors is low are more sensitive to neoadjuvant chemotherapy with higher pathological response. To sum up, it is helpful for improving the effects of neoadjuvant chemotherapy and patients' diagnosis if the expression level of ER is regulated with the aid of TCM in different stages of treating breast cancer.

TCM is effective for bidirectional regulation of expression of hormone receptors. Some recent research have found that the TCM which can upregulate the expression level of hormone

receptors for breast cancer include Quercetin hydrate, Psoralen, Shikonin and Shugan-Liangxue prescription. Among these, both Quercetin hydrate and Psoralen can increase ERα mRNA and protein expression levels of ER-positive breast cancer cells [1]. There are still very few research reports about TCM that can downregulate the expression levels of ER and PR in breast tissues. Yuzhong et al. [2] have discovered that Shikonin is a little effective for inhibiting growth of MCF-7 breast cancer cells. The expression of ER in MCF-7 cells treated by Shikonin is decreased. Shugan-Liangxue prescription (including Comfrey, Tree peony bark and Bupleurum) also can slightly inhibit the expression of ER mRNA and reduce the expression of ERα [3]. The specific roles of Purple gromwell and Shugan-Liangxue prescription in improving the effects of neoadjuvant chemotherapy and TCM with the same effects as estrogen in improving patients' diagnosis remain to be further verified by clinical research with large sample size.

Suppressing Expressions of Related Factors of Cell Proliferation

HER-2/neu is a proto-oncogene, and its over-expression often reveals that tumor cells proliferate actively, which promotes tumor metastasis and recurrence, thereby shortening patients' overall survival. On the other hand, patients with breast cancer are quite responsive to neoadjuvant chemotherapy when their HER-2 expression is high. In particular, this gene is effective for predicting therapeutic effects of chemotherapeutic drugs like Anthracyclines [4,5]. Ki-67 is a nucleoprotein antigen, while its high expression indicates active cell proliferation and high sensitivity to neoadjuvant chemotherapy, especially anthracyclines related regimes [6]. However, the prognosis is usually poor among patients whose expressions of Ki-67 are high. Downregulating expressions of factors about such cell proliferation may inhibit proliferation of breast cancer cells, reduce metastasis/recurrence, strengthen long-term therapeutic effects of neoadjuvant chemotherapy and improve patients' prognosis. Nevertheless, patients' responses to neoadjuvant chemotherapy may be impacted once the expressions of factors about cell proliferation are inhibited. Hence, the problem which how to seek an optimal balance between patients' response to neoadjuvant chemotherapy and long-term therapeutic effects is worthy of attention. To achieve such a balance, it is firstly necessary to explore some kind of TCM which can inhibit expression levels of *HER-2/neu* and Ki-67.

The TCM which can downregulate the expression level of HER-2 are Rhein and Ruyanning prescription (including Ginseng, Astragalus, Atractylodes, *Poria cocos* and so on) according to the results of the present studies. The research [7] has discovered that Ruyanning is helpful for reducing HER-2 expression of breast cancer by promoting apoptosis of cancer cells. The Ruyanning prescription, mainly made from drug strengthening body resistance, is effective for eliminating the pathogenic factors. Rhein can also downregulate the expression level of HER-2 mRNA in breast cancer cells, bring the roles in inhibiting the expression of HER-2 into play from the perspective of transcriptional level [8]. The TCM that may

inhibit expressions of Ki-67 is mainly divided into two categories as follows. 1. Blood-activating and stasis-resolving medicines: For instance, Zedoary turmeric oil [9] can decrease the proliferative activity of breast cancer epithelial cells and inhibit the expression of Ki-67. 2. Tonic drugs: Zhang et al. [10] have reported in their research that the combined use of Ginsenoside Rg3 and cyclophospamide is more effective for inhibiting Ki-67 of breast cancer than pure application of cyclophosphamide. Without more significant toxicity or side effects, it plays more durable and stable roles in suppressing tumors. Rhodiola [11] is also effective for protecting against breast cancer to certain extent, as the percentage of Ki-67, as an indicator of the proliferation of breast cells, declines significantly inside transplanted tumors after the treatment with this drug.

Suppressing Expression Level of Tumor Apoptotic Suppressor Genes

It is important for inhibiting development of tumors by inducing apoptosis of tumor cells, and most chemotherapeutic drugs remove tumor cells by inducing apoptosis. The tumor development, effects of chemotherapeutic drugs and patients' prognosis and so on are closely connected with expression level of genes about apoptosis of tumor cells. In exploring genes about apoptosis of tumor cells, *Survivin*, *P53* and *Bcl-2* are treated as representative genes. *Survivin* is a gene that can suppress apoptosis. It is associated with the differentiation of proliferation and metastasis of tumor cells, so chemotherapy is more effective for patients whose expression of *Survivin* is negative and weakly positive than those with positive and strongly positive expression of *survivin* [12]. *P53* is classified into wild and mutant genes, among which the former may promote apoptosis, while latter can protect tumor cells from the apoptosis induced by chemotherapeutic drugs and thus reduce the effects of chemotherapy [13]. *Bcl-2* is a gene that can suppress apoptosis, and a certain research [14] has shown that the response rate is higher in patients with *Bcl-2* negative tumors after chemotherapy. Therefore, if some drugs can be found for downregulating expression level of such genes, it will be possible to further increase sensitivity of tumor cells to chemotherapy, inhibit proliferation of tumor cells, induce apoptosis of tumor cells and improve patients' prognosis. Furthermore, these drugs shall have few side effects, or else they can't act in combination with chemotherapeutic drugs, but even further aggravate body burden and induce normal apoptosis. To achieve above goals, it is especially meaningful for researching TCM with the above characteristics.

Over the last few years, some TCM has been discovered to have the aforementioned features. 1. Suppressing expression of *survivin*: The periplocin extracted from cortex periplocae can also inhibit proliferation of breast cancer cells, downregulate their apoptosis and suppress the expression of *survivin* mRNA [15]. 2. Bidirectional regulation of *P53*: TCM can upregulate the expression level of wild *P53* and somewhat inhibit the expression of mutant *P53*. For example, Bittersweet Herb can significantly upregulate the mRNA expression of *p53* in breast

cancer cells and induce the apoptosis of these cells [16]. The study of TCM which can regulate mutant *P53* mainly focus on Blood-activating and stasis-resolving medicines. Some studies [17,18] showed that both Guizhifuling pill and Tanshinone can downregulate the expression of mutant *P53*. 3. Suppressing expression of *Bcl-2* genes: As extracted TCM, Baicalin is mainly effective for suppressing expression of *Bcl-2* in breast cancer cells, inhibiting the proliferation of these cells and inducing cell apoptosis, while the apoptosis rate increases with the increase in the concentration of Baicalin [19]. Being effective for suppressing the expression of *Bcl-2*, flavonoids from seed residues of *Hippophae rhamnoides* L may induce typical morphological changes of apoptosis in breast cancer cells [20].

Suppressing Expression of Factors Related to Tumor Metastasis

Metastasis of cancer cells is usually one of important reasons why neoadjuvant chemotherapy fails in breast cancer. Besides, metastasis and recurrence of breast cancer are correlated to multiple biological indicators. Therefore, an attempt is made to look for TCM that may inhibit the expression of these biological indicators, in order to improve effects of neoadjuvant chemotherapy and decrease recurrence and metastasis of tumors. Research has suggested that CD44, closely connected with metastasis and prognosis of breast cancer, creates micro-environment for proliferation, metastasis and invasion of tumor cells. CD44 can be conferred as a predictive index of chemotherapy drug resistance of breast cancer patients, and chemotherapy may enrich CD44 positive breast cancer cell [21]. Therefore, we try to find some TCM which can inhibit the expression of such biological indexes, so as to improve curative effects of neoadjuvant chemotherapy and reduce tumor metastasis and recurrence. Guizhi Fuling pills can decrease the expression level of CD44 and increase the efficacy of cyclophosphamide [17]. As an enzyme for degrading basal plasma membrane, Cathepsin-D plays important roles in tumor metastasis. Its low expression can be used as an indicator for predicting therapeutic effects of anthracycline-based neoadjuvant chemotherapy, and chemotherapy is much more effective for Cathepsin D-negative patients than those Cathepsin D-positive patients [22]. A certain report has claimed that [23] "Runing II", a Chinese herbal compound (including *Radix astragali*, *Radix pseudostellariae*, *Coix* seed, *Tulip bulb* and so on), may suppress the expression of Cathepsin-D, can inhibit metastasis of breast cancer and improve effects of chemotherapy.

Reversing Multidrug Resistance of Tumors

As an important barrier to neoadjuvant chemotherapy for breast cancer, Multidrug Resistance (MDR) has serious impacts upon effects of neoadjuvant chemotherapy, and reversing multidrug resistance of breast cancer has been a hot research topic over the past few years. However, to reverse the multidrug resistance, it is firstly necessary to know about their pathological mechanisms, and the MDR of breast cancer is induced by multiple mechanisms. Over the past few years, P-gp (i.e. product of MDR1) and TOPO-II have been found to be closely connected with drug resistance of breast cancer. P-gp expression is a determinant factor in predicting response to neoadjuvant chemotherapy, and the chemotherapy is usually less effective in P-gp positive patients than P-gp negative ones [24]. Patients whose TOPO-II expressions are high are more sensitive to anthracycline-based regimes with better pathological responses [25]. Hence, the efforts shall be made to increase breast cancer s' sensitivity to anticancer drugs, reverse multidrug resistance of breast cancer and improve effects of chemotherapy by regulating indicators with TCM based on above two biological indicators.

The research suggests that blood-activating and stasis-resolving medicines are discovered to be major TCMs that can suppress expression of P-gp and promote expression of TOPO-II, such as Emodin, Ligustrazine, and Cepharanthine hydrochloride. Being effective for significantly downregulating the expression of P-glycoprotein, Emodin can persistently reverse the multidrug resistance of MCF-7/Adr breast cancer cells [26]. Ligustrazine can hinder doxorubicin from promoting the expression of P-gp [27]. Cepharanthine hydrochloride is effective for reversing the multidrug resistance of MCF-7/ADR breast cancer cells at non-cytotoxic concentration. When its concentration is 4 µmol/L, it can strengthen catalytic activity of DNA Topo-II in MCF-7/ADR cells [28] and weaken self-repairing capabilities of DNA after cellular injuries, so as to increase sensitivity of recovered drug-resistant cells to chemotherapy drugs and improve effects of chemotherapy

Others

There are numerous and various research reports about indicators concerning therapeutic effects of neoadjuvant chemotherapy for breast cancer. For example, research findings have suggested that [29] the probabilities of clinical complete remission and pathologic complete response are significantly lower in patients whose expressions of human Telomerase Reverse Transcriptase (hTERT) mRNA and protein are positive than those with negative expressions. After MCF-7 cells are treated with *Rhizoma curcumae* oil, their proliferation and viability get to decrease [30], so does the expression level of hTERT. In addition, some reports have indicated that COX-2 (Cyclo-oxgenase 2), *BRCA1* gene, *FHL1* gene, *C-myc* gene, CXCR4 (i.e. chemokine receptor), MCM protein (minichromosome maintenance protein), Tau protein and NF-kB (nuclear transcription factor) are related to the effects of neoadjuvant chemotherapy. Besides, the roles of TCM in these biological indicators remain to be further investigated.

Problems and Prospects

Existing problems

Although it has been proven in many clinical studies that TCM can improve the effects of neoadjuvant chemotherapy for breast cancer, its mechanism of actions is still unclear. It is possible to open up new prospects for illustrating the

mechanism of action of TCM and their practical integration with Western medicine in clinical practices from the perspective of molecular biology. However, there are still several problems as follows: 1. TCM is generally effective for the human body in terms of multiple targets and factors. It is just because of such complexity of TCM that it is still in an initial stage of exploring the molecular mechanism of action for TCM to improve the effects of neoadjuvant chemotherapy for breast cancer. 2. A common problem is faced no matter in studying indicators about effects of neoadjuvant chemotherapy for breast cancer or investigating the roles of TCM in these indicators. To be exact, most of these studies generally cover a small sample size, which is an important cause of credibility. At present, it is generally acknowledged that the effects of neoadjuvant chemotherapy are associated with multiple genes and factors. Hence, more efforts shall be made to investigate selection of above molecular biological indicators and combined application of several indicators. 3. Although it has been demonstrated in clinical practices that some TCM can strengthen effects of neoadjuvant chemotherapy, these studies are not neither reproducible nor credible without sufficient objective indicators. Hence, to select preparations of TCM that can really improve chemotherapy for breast cancer through their molecular mechanism of action, or to guide the use of TCM according to above molecular biological indicators, clinical research with large sample size remains to be performed for further demonstration.

Direction of future study

There is still a long way to go for combining TCM with neoadjuvant chemotherapy in the treatment of breast cancer patients. Efforts can be made from the following aspects. 1. With research about molecular biology was constantly deepened, it has become possible to build models for predicting effects of neoadjuvant chemotherapy for breast cancer and perform individualistic chemotherapies with different regimes according to different biological characteristics of breast cancer. Such thought of individualistic chemotherapies is coincidentally in line with treatment based on syndrome differentiation in TCM. Therefore, these microscopic molecular biological indicators are one of evidences for treatment based on syndrome differentiation. For instance, for patients whose expressions of Survivin protein are positive or strongly positive, an appropriate amount of cortex periplocae can be used based on syndrome differentiation and treatment, so as to downregulate the expression level of *Survivin* and increase therapeutic effects. TCM, which can promote blood circulation and remove blood stagnation, are relatively effective for regulating multiple factors such as hormone receptors, Ki-67 and P-glycoprotein. With the certain help for neoadjuvant chemotherapy, which is amazingly similar to the view of TCM that phlegm and blood stagnation are major pathological causes of breast cancer. Hence, perhaps some drugs for promoting blood circulation and removing blood stagnation can be used in the whole process of chemotherapy. 2. Multi-center clinical research of a large sample size needs to be performed to further demonstrate the

combined roles of TCM and neoadjuvant chemotherapy. Meanwhile, it is necessary to explore TCM from multiple perspectives and levels with modern molecular biological technologies, particularly various regulatory roles of compound TCM. In this way, the action mechanism of TCM for aiding chemotherapies can be explored more systematically and scientifically. 3. Relationships between syndrome types of TCM and neoadjuvant chemotherapy for breast cancer remain to be further examined and strengthened. TCM is based on the syndrome types, so it is critical to enhance the exploration of the syndromes. For instance, attempts can be made to investigate if biological indicators are associated with syndrome types of TCM and prognosis of different syndromes. TCM attaches importance to treatment based on syndrome differentiation and overall concepts. Particularly, it is important to adopt "theory of visceral manifestations". In order to make the theory of TCM become more acceptable, we can illustrate TCM with modern sciences and technologies, and integrate TCM with modern sciences and technologies is an important step for having TCM recognized by people of the world.

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Conflict of Interests

The authors declare that they have no conflict of interest.

Claim

We claimed that this paper was original and would not have any financial interest in a company or its competitor, and that all authors meet criteria for authorship.

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*Correspondence to

Zhang Xiping

Department of Breast Surgery

Zhejiang Cancer Hospital

PR China