DOI: 10.53469/jcmp.2024.06(11).32

Research Progress on the Impact of Traditional Chinese Medicine Treatment on Tumor Microenvironment

Bin Jiang[1], Zhen Wang[1], Jia Yuan[1], Jianfeng Quan[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Tumor microenvironment mainly includes non-tumor cells, cytokines, chemokines and extracellular matrix. It is an important part of anti-tumor immunity and plays a vital role in the formation and invasion of tumors. Anti-tumor treatment is in line with the concept of "Fuzheng anti-cancer" of traditional Chinese medicine, and the regulation of anti-tumor traditional Chinese medicine on the tumor microenvironment can be expounded based on the body's immunomodulation mechanism. It discusses strengthening the body's immune barrier, curbing tumor growth from the source, and reversing the microenvironment that is conducive to tumor survival; it can guide the normalization of tumor blood vessels to reduce the probability of tumor infiltration, metastasis and recurrence; and improve the quality of life of the host by reducing adverse reactions caused by therapeutic drugs.***

Keywords: Traditional Chinese medicine, Traditional Chinese medicine, Tumor microenvironment, Research progress**.**

1. Introduction

Tumor treatment is the most troublesome medical problem in the world today. The reason is that traditional tumor treatment methods such as surgery, radiotherapy and chemotherapy will produce certain toxic side effects and drug resistance, which greatly reduces the quality of life of patients. Therefore, seeking better treatment methods is an urgent problem to be solved [1]. In recent decades, immunotherapy has been widely used in tumor therapy and is regarded as an important anti-tumor weapon. Early anti-tumor research only focused on the tumor itself. With the deepening of the research, the focus was gradually shifted to the tissue environment around the tumor, that is, the tumor mi-croenvironment (TME). There is evidence that the tumor microenvironment is an important part of anti-tumor immunity, and may also become a new target for tumor immunotherapy [2]. The ideology of traditional Chinese medicine is extensive and profound, and its role in tumor treatment is also receiving widespread attention. Research shows that traditional Chinese medicine can act on multiple targets in the tumor microenvironment, such as immune cells infiltrated in the tumor microenvironment, tumor-associated macrophages (TAMs), tumor-associated fibroblasts (tumor-Associated fibroblast, CAFs), cytokines and immune regulatory points effectively treat tumors, reduce the occurrence of complications and improve prognosis, bringing new hope for tumor treatment.

2. Overview of Tumor Microenvironment

The concept of tumor microenvironment can be traced back to the connection between inflammation and tumor proposed by VIR**-**CHOW in 1863, and the theory of "seed and soil" proposed by PAGETS in 1889 [3]. The tumor mi-croenvironment is the soil in which tumor cells live. The tumor microenvironment provides a place and nutrients for the growth of tumor cells, and also provides vascular channels for the distant metastasis of tumor cells. The evolution of tumors can generally be divided into four stages: occurrence, promotion, development and metastasis, so the tumor microenvironment is a comprehensive dynamic system [4]. TME is mainly composed of non-tumor cells, cytokines, chemokines and extracellular matrix. Non-tumor cells mainly include vascular endothelial cells, lymphatic endothelial cells, inherent immune cells (TAMs, DCs, NK cells, etc.), acquired immune cells (T and B lymphocytes) and various interstitial cells, such as CAFs [5]. Tumor microenvironment is the determinant of tumor heterogeneity. Tumor cells and the surrounding microenvironment are dependent on each other and affect each other: tumor cells can release extracellular signals and act on the tumor microenvironment to produce immune tolerance. Immune cells infiltrated in the microenvironment can also kill tumor cells and prevent them from continuing to proliferate and metastasize [6,7].

3. The Theory of Traditional Chinese Medicine Regulating the Tumor Microenvironment

Traditional Chinese medicine has the theory of yin-yang balance and the competition between good and evil for the formation of tumors. The Neijing wrote: "The righteousness exists, and evil cannot be done" and "If evil is gathered together, its qi will be empty" [8]. Righteousness is equivalent to the immune function of the body. When immune defense, monitoring and clearance functions are normal, the body can resist the invasion of tumor cells. When immune cells are insufficient or tumor cells escape immunely, the righteous qi in the body cannot defeat evil spirit, and tumor cells will proliferate and migrate. In "Su Wen · Baomingquanxinglun", it is written: "Life is tangible and does not leave yin and yang." The balance of yin and yang refers to the mutual adjustment of yin and yang, and the dynamic balance is achieved in opposition, so that the body can identify "self" and exclude "different" to maintain the stability of immune function. Traditional Chinese medicine reshapes the tumor immune microenvironment by acting on cells or cytokines in the tumor microenvironment and strengthens the body's anti-tumor immune response to treat tumors.

4. Immune Regulation of Traditional Chinese Medicine on the Microenvironment of Tumors

4.1 Improve the Host Immune Barrier and affect the Tumor Microenvironment

The formation of tumor microenvironment, tumor-immune circulation, immune typing concept. The formation of tumors is formed by the accumulation of positive qi and internal deficiency under the overall situation, mixed with different degrees of cold coagulation, qi stagnation, blood stasis or wet accumulation, phlegm knot, heat poison and other secondary evils. In view of cancer-toxicity and different immune microenvironments, doctors need to guide the treatment with the concept of "treating the deficiency and taking care of deficiency, and not forgetting the truth". As early as the Haung Di Nei JING, it was proposed: "If righteousness exists, evil cannot be done [8]" and "If evil is gathered together, its qi will be empty [9]". These two concepts can summarize the pathogenesis of most diseases. As far as tumor patients are concerned, their immune system is not necessarily low as a whole, but the effect on tumors is inhibited, that is, immune imbalance causes the microenvironment reversal of the body's immunity, which is consistent with the original intention of today's tumor microenvironment immunotherapy for the body's immune balance mechanism. Li Zhongzi, a doctor, mentioned in "Yi Zong Bi Du · Jiju" [10]: "Those who accumulate, the positive qi is insufficient, and then the evil qi is in it". He pointed out that the lack of righteous qi, that is, the positive qi of the human body is in a relatively disadvantaged condition. Cancer and other evil qi then invades the body and resists positive qi, and the disease accumulates and accumulates into cancer tumors. The "Yi Zong Bi Du · Jiju" also points out that "the accumulation of regularity" lays a theoretical foundation for the righteous treatment of future generations. In the past, the medical community's treatment of tumors emphasized the attack on local tumors, ignoring the survival period, and the patient's life expectancy and quality of life were not effectively guaranteed. The reason was that insufficient attention was paid to the maintenance of the body's righteousness. Liu Jiaxiang, a contemporary master of traditional medicine, has reversed the direction of cancer treatment based on "attack and killing", advocating that positive deficiency is the basis, and cancer poison entrenched is the main mechanism for the occurrence and development of cancer tumors. The host's righteous qi is weak, and local cancer poison and righteousness are implicated with each other, causing yin and yang tolerant, not living in the camp, and the viscera cannot take charge of their duties, and the virtuality is mixed. Cancer can't last for a long time, and if it is yang and yin, it will form a local yin, and it is easy to metamorphosis and metastasis. Professor Liu Jiaxiang proposed a anti-cancer method with the goal of "removing evil" on the premise of "supporting right". He emphasized that anti-tumor traditional Chinese medicine is a kind of traditional Chinese medicine that under the treatment of anti-cancer, under the treatment of anti-cancer, it can eliminate the etiology of tumor growth microenvironment, inhibit tumor growth, and achieve a kind of traditional Chinese medicine to achieve the role of tumor microenvironment of tumor microenvironment. Professor Liu called for the treatment of tumor should be balanced and pay attention to the microenvironment.

4.2 The Effect of Traditional Chinese Medicine on Immune Organs

The immune organs of the human body can be divided into central immune organs and peripheral immune organs. The former includes the thymus, bone marrow, etc., which focus on promoting the production and development of immune cells and mature differentiation. The latter includes spleen, lymph nodes, mucosal-related lymphatic tissue, etc., which is defined as the primary base for the gathering of mature lymphocytes. The two are interconnected through blood circulation and lymphatic circulation, which has a crucial impact on the body's immune function. When Li Yuchuan et al. [12] explored the effect of Bazhen Decoction combined with cyclophosphamide in the treatment of S-180 sarcoma in mice, they found that the 6-day and 10-day cyclophosphamide and the above two groups combined with Bazhen soup respectively had certain effects on the treatment of S-180 sarcoma. Among them, the 6-day cyclophosphamide combined with Bazhen Decoction group on the protection of the spleen and The thymus index and peripheral white blood cell count are higher than those of other treatment groups. It can be seen that the combination of traditional Chinese and Western medicine with anti-tumor immunotherapy needs to be combined with appropriate chemotherapy course time to exert greater therapeutic effect. Tsioumekou et al. [13] introduced licorice into sodium alginate nanogel particles to build a multifunctional drug delivery carrier, which can not only overcome the limitations of the traditional drug delivery system in cancer treatment, but also increase the intracellular concentration of drugs in cancer cells, while avoiding toxicity to normal cells and triggering The immune inflammatory response of macrophages can reduce the effect of rapidly cleaning of autologous T cells that activate macrophages. Low molecular weight licorice polysaccharide has an immunomodulatory effect on mice with CT26 tumor. Glycicin combined with amoxycillin can change the immune tumor microenvironment. To a certain extent, it can not only prevent immune organs from being invaded by tumor cells, but also enhance the immune function of immune organs.

4.3 The Effect of Traditional Chinese Medicine on Tumor-related Cytokines

Modern research shows that [14,15] the metabolism of malignant tumor cells needs more energy supply than normal cells, so it often leads to hypoxia, which is a common and specific phenomenon in cancer cells. Tumor-related cytokines include mononuclear macrophage system, lymphocyte subgroups, interleukin, tumor necrosis factor and fibroblasts, transformation growth factor-beta family, growth factor, etc. In order to adapt to this hypoxia state, the collection of immunosuppression and metabolic secretion of the body have also been correspondingly intensified, two-way regulation of tumor microenvironment, affecting tumor microangiology and lymph metastasis power of tumor cells. The tumor microenvironment is affected by hypoxia-inducing factor-1α. The hypoxia state can lower the expression of autophagy-related molecules Beclin 1 and LC3B [16], while anti-tumor Chinese medicine can reduce the hypoxia in the tumor microenvironment and induce autophagy in tumor cells

or directly induce cell autophagy, change the instability of the tumor microsatellite fob, and block its growth, differentiation and effect.

4.4 Traditional Chinese Medicine Regulates Negative Immunomodulation

Anti-tumor traditional Chinese medicine can mediate immune tolerance by regulating the local tumor immune microenvironment to affect immunotherapy, but not all tumor patients with various immune types can benefit. In the tumor microenvironion, the activation and inhibition of T cells is in an abnormal pattern. In theory, most people's tumor immune circulation is complete until T cells kill tumor cells, which is effectively inhibited by PD-1. The body's negative immunomodulation is affected by the expression of PD-1 receptors by tumor cells. PD-1 binds to the target PD-1 on T cells to inhibit T cell proliferation and reduce the cytotoxicity of lymphocytes. The tumor wins a prime time period of rapid differentiation, proliferation and even metastasis. Once the PD-L1/PD-1 immune regulation axis is blocked, the previously existing T cells of immune immunity and immunoinflammatory patients can quickly restore their effector function. Han et al. [17] found that triterpene saponins in goose palm grass, a tadpole plant, have an anti-liver cancer cell proliferation effect. By regulating the release of immune effect cells and inflammatory mediators, they have a high affinity with them, which can drive CD28 molecules on cytotoxic T lymphocytes and compete with specific antigens on the surface of tumor cells. The B7 molecule on the binding antigen presenter cell and the negative regulation of the expression of PD-1/PD-L1, ERK1/2, p38M, JNK and STAT3 are related, which has the advantage of reversing the tumor microenvironment. Liang Ying et al. [18] studied the mechanism of Yipi activating blood prescription to regulate the combination of B7-H1 and PD-1 to prevent recurrence after hepatocellular carcinoma in rats. After 4 weeks of treatment, the recurrence of naked mice CD4+ and CD4+/CD8+ in the probiotics in the spleen and 5-fluorouracil group increased significantly in peripheral blood and spleen, and the level of CD8+ cells decreased significantly.

4.5 Change the Microenvironmental Instability of the Tumor and Induce the Normalization of Tumor Blood Vessels

4.5.1 Tumor heterogeneity and tumor microenvironment instability

Tumor heterogeneity is caused by the instability of the genome. It is precisely because of this unstable immune editing that leads to the evolution, upgrading and mutation of tumor cells. The tumor mutation load drives tumor cells prone to drug resistance. Therefore, delaying drug resistance and buying time for the next step of treatment has become a new bottleneck in the management of the whole process of tumor. The angiogenesis mechanism plays an important role not only in a wide range of physiological conditions such as embryonic development, wound healing process, but also in many pathological evolutions such as tumor growth and chronic inflammatory transformation. The gene expression of vascular endothelial cells is relatively stable, which makes it relatively difficult for tumor cells to develop drug resistance. Therefore, the treatment of anti-tumor angiogenesis in the use of drugs has always attracted much attention. The development of angiogenesis drugs that affect tumors can be roughly divided into three stages. The first stage is the hypothesis that tumor growth depends on new angiogenesis. In the 1980s, Judah Folkman believed that when the tumor microenvironment is unbalanced and affected by the paracrine or self-secretion effect of vascular endothelial cells, tumor neovascularization blood vessels continue to infiltracture under the malignant growth cycle, and the immunological changes induced by tumor cells will also induce the proliferation and migration of endothelial cells. Tumor neovascularization blood vessels quickly absorb nutrients from normal cells, initiate a counterattack on local tumor-related immune cells, inhibit the proliferation of immune cells, and from an objective point of view, forming a microenvironment conducive to tumor invasion and metastasis [19]. The second stage is to strongly inhibit tumor angiogenesis. Under the premise of the above theory, inhibiting tumor angiogenesis has become the main direction of a large number of clinical treatment and academic research, but with the treatment effect, it brings six major side effects such as bleeding, gastrointestinal perforation, delayed wound healing, hypertension, cardiotoxicity, proteinuria [20], which often lead to drugs Reduce the dose or stop using it. Therefore, it is urgent to find new diagnosis and treatment ideas for tumor blood vessels. The third stage is to guide the normalization of tumor blood vessels.

4.5.2 Guide the normalization of tumor blood vessels and tors the tumor microenvironment

At present, researchers are trying to change ideas from completely eliminating tumor angiogenesis to guiding the normalization of tumor blood vessels by regulating the tumor microenvironment. In the occurrence of cancer, abnormally expressed inflammatory factors can induce the transformation of surrounding normal cells to cancer cells in the early microenvironment, which is a sign of precancerous lesions. At the same time, it also promotes the differentiation and proliferation of new tumor blood vessels, infiltrates the surrounding normal tissues, and is more likely to transfer to the distance. Among them, IL-2, IL-4, IL-6 and TGF-β also participated in this process. Pan Huafeng et al. [21] observed the effect of the traditional Chinese medicine gastritis I and the model group on the ratio of IL-4 to tumor necrosis factor-α, IL-6 and other secretion of gastric precancerous rats. The study found that by regulating gastric mucosal inflammation and immune microenvironment, gastritis I can regulate the activation of gastric mucosal stromal lymphocytes and monocytes, regulate the secretion of gastrointestinal hormones, and realize the repair of functional cell damage in gastric mucosal epithelial tissue, thus reversing gastric precancerous lesions.

4.6 Reduce Toxic Side Effects and Improve the Quality of Life

The ultimate goal of tumor treatment is to prolong survival and improve the quality of life rather than simple tumor shrinkage. The body's immune response to tumors and the toxic side effects of antitumor drugs are important factors

affecting the patient's treatment completion rate and the improvement rate of quality of life. And the disappearance or relief of cancer-related clinical manifestations, to a certain extent, gives patients and their families a positive psychological suggestive effect. Therefore, anti-tumor traditional Chinese medicine provides a possibility for the transformation of tumor diseases into chronic diseases. Huang Sha et al. [22] By studying the malignant peritoneal effusion caused by liver depression and spleen deficiency syndrome caused by advanced stomach cancer, combined with chemotherapy, it is revealed that the pathogenesis of malignant peritoneal effusion belongs to the abnormality of fluid, water and moisture stops coke, while anti-swelling and tumor suppression has the effect of soothing the liver and strengthening the spleen, facilitating hydration and humidification, so that the qi moves and the abdomen is full. During the treatment, the toxic and side effects caused by chemotherapy such as nausea, vomiting and diarrhea in the treatment group were reduced to a lesser extent than in the control group, and the liver and kidney function was also significantly improved. Complications such as water and salt metabolism imbalance and hypoproteinemia that may be caused by the drainage of peritoneal effusion can also be alleviated.

5. Traditional Chinese Medicine Treatment of Tumor-related Macrophages in Tumor Microenvironment

Tumor-related macrophages are the most characteristic cells in the tumor microenvironment. They can form 50% of tumor masses and play an active role in the early cancer to metastasis of tumors [23,24]. TAMs can enhance the ability of tumor cell invasion and metastasis, angiogenesis and extracellular matrix reconstruction, and are regarded as an important monitoring index of anti-tumor immunity. Tumor-related macrophages can be polarized into two subtypes: classically activated macrophages (M1) and alternately activated macrophages (M2). M1 can present antigens and promote Th1 immune-killing tumor cells. However, most TAMs in TME tend to polarize to M2 type. M2 macrophage can induce Th2 immunity to support tumor growth and invasion [25]. Therefore, researchers are working on immunomodulators that polarize TAMs into M1. Mushroom beta-dextose extract from mushrooms can increase M1 and reduce M2 tumor tissue in Lewis lung cancer mice, thus strengthening the anti-tumor immune response [26]. The extract of baicalin can induce the polarization of TAMs to M1, promote the production of pro-inflammatory cytokin in tumors, and inhibit tumor growth in mouse liver cancer models. PANG et al. [27] studies show that lung soup composed of mulberry leaves, schisaweizi, ground yellow and ginseng can inhibit the expression of IL-10 and PD-1 both inside and outside the body, and relieve the clinical symptoms caused by non-small cell lung cancer. The phyllic acid extract polysaccharide extracted from fungi activates tumor-related macrophages and enhances their phagocytic ability through the NF-κB signaling pathway, so that they can exert their immune function and inhibit the proliferation of tumor cells [28]. At present, a collaborative chemotherapy immunotherapy has emerged, using maca polysaccharde (MPW) and its derivatives (C-macapolysacchartde, C-MPW) and doxorubicin as immunomodulators to jointly treat tumors. The study found that MPW and C-MPW polarized TAMs to M1 through NF-κB, STAT1 and STAT3 signaling pathways, exerting anti-tumor immunity, inhibiting tumor invasion and reducing toxicity [29].

6. Traditional Chinese Medicine Treatment of CAFs in Tumor Microenvironment

CAFs are the main source of cytokines and chemokines such as IL-6, TGF-β and CXCL-12 [30]. CAFs can directly inhibit the function of immune cells or induce the production of M2 tumor-related macrophages and Th2 cells. They can also promote extracellular matrix regeneration, epithelial interstitial transformation, and angiogenesis to indirectly inhibit immune response [31]. Curcumin originates from the roots of turmeric, which is a natural polyphenol compound. Studies have found that curcumin reduces the invasion ability of pancreatic cancer cells by targeting CAFs [32]. The xanthrine polysaccharide extracted from jade bamboo can inhibit the growth of CAFs in prostate cancer, thus inhibiting tumor migration [33]. Sipi soup (SPS) is made from root skin water extracts such as bitter ginseng, weeping willows, mulberry trees and bitter almonds. Studies such as ZHOU have shown that [34] SPS prevents the inflammatory process by inhibiting the activation of CAFs and reducing the expression of HIPK1-AS, thus preventing the development and metastasis of cervical cancer.

7. Brief Summary

The tumor microenvironment provides a living place and nutrients for tumor cells, and provides a channel for their invasion. It has the function of immune monitoring, and the treatment of the tumor microenvironment as a whole coincides with the treatment concept of traditional Chinese medicine. With the rapid development of immunology, the use of traditional Chinese medicine for immunotherapy will bring new possibilities to the treatment of tumors. Using TME as a research target can show the advantages of holistic treatment of traditional Chinese medicine. The application of traditional Chinese medicine to immunotherapy can produce good therapeutic effects, reduce adverse reactions, improve prognosis, prevent drug resistance, reduce pain caused by cancer, and prolong the survival time of patients. However, the specific mechanism of traditional Chinese medicine for the treatment of tumors is still unclear, and further in-depth research is needed. Combining the theory of traditional Chinese medicine with modern scientific research methods to explore the specific anti-tumor mechanism, so that traditional Chinese medicine can continue to innovate and develop inheritance is the direction of future efforts.

References

[1] GAO Ming, WANG Tong, YANG ChunYu, et al. Latest development of traditional Chinese medicine immunotherapy based on tumor microenvironment[J]. Chinese Journal of Immunology, 2021, 7(4): 506-510.

[2] WU T, DAI Y. Tumor microenvironment and therapeutic response[J]. Cancer Lett, 2017, 387: 61-68.

[3] IN M Z, JIN W L. The updated landscape of tumor microenvironment and drug repurposing[J]. Signal Transduct Target Ther, 2020, 5(1): 166.
[4] KLEMM F, JOYCE J A. Microenvironmental regulation of therapeutic response in cancer[J]. Trends Cell Biol, 2015, 25(4):198-213.
[5] ZHANG Y, HAN X, NIE G. Responsive and activable nanomedicines for remoedling the tumor microenvironment [J]. Nat Protoc, 2020.
[6] LIN W F, LU J Y, CHENG B B, et al. Progress in research on the effects of traditional Chinese medicine on the tumor microenvironment[J]. J Integrat Med, 2017, 15(4): 282-287.
[7] LIN Yi, TAO Li. Theoretical conception of traditional Chinese medicine for metastasis of colorectal cancer[J]. Shanghai Journal of Traditional Chinese Medicine, 2020, 54 (2): 6-9.
[8] Huang Di Nei Jing · Su Wen · Ci Fa Lun [M]. 2nd edition. Kunming: Yunnan Education Publishing House, 2011: 255-263.
[9] Huang Di Nei Jing · Su Wen ·Ping Re Bing Lun[M]. 2nd edition. Kunming: Yunnan Education Publishing House, 2011:106-108.
[10] Li Zhongzi. Zong Yi Bi Du·Juji[M]. Tianjin: Tianjin Science and Technology Press, 2012: 206-207.
[11] Liu Jiaxiang. Treating Cancer by Strengthening Vital Qi-A Inherited and Inovative Method with Integrating Chinese and Western Medicine[J]. Chinese Journal of Integrated Traditional and Western Medicine, 2019, 39(1):10-12.
[12] Li Yuchuan, Liu Yujie, Zhang Yuanzhe, etc. Experimental study of Bazhen soup combined with chemotherapy drugs to treat S-180 sarcoma in mice[J]. Lishizhen Medicine and Materia Medica Research, 2016, 27(12): 2857-2849.
[13] TSIOUMPEKOU, CUNHA SI, MA H, et al. Specific targering of PDGFRβin the stroma inhibits growth and angiogensis in tumors with high PDGF-BB expression [J]. THERANOSTICS, 2020, 10(3): 1122-1135.
[14] WANG Y, JIANG H, LUO H, et al. An IL-4/21 linverted cytokine receptor improving CAR-T Cell potency in immuno suppressive solid tumor microeniranment [J], Frontiers in Immunology, 2019, 10:1691.
[15] GRETEN F, GRIVENNIKOVS. Inflammation and cancer: triggers mechanisms, and consequences[J]. Immunity, 2019, 51(1): 27-41.
[16] Cao Huiqiong, Cai Qinghong. The relationship between the expression of hypoxia-induced factor-1αand vascular endothelial growth factor and gastric cancer vascular production[J]. Jilin Medical Journal, 2020, 41(1): 184-185.
[17] HAN L, YAOS CAOS, et al. Triterpenoid saponins from anemne fiaccida suppress tumor cell proilferation by regulating MAPK, PD1/PDL1, and STAT3 signaling pattways and altering cancer metbolis[J]. 2019, 12: 10917-10930.
[18] LIANG Ying, CHENG Gang, HUANG Denggao. Preventive Mechanism of Yipi Huoxue Recipe on Postoperative Recurrence for Rats after Hepatectomy by Regulating B7-H1/PD-1Signal Pathway[J]. Journal of Sichuan of Traditional Chinese Medicine, 2019, 37(8): 24-27.
[19] Zheng Jimei, Wu Feipeng, Song Sucai, et al. The Progress of Research on Anti-Tumor Chinese Medicine on Tumor Micro-Environment Immune Regulation[J]. 2020, 16(6): 185-189.
[20] KIM MS, KIM H, AHNEK, et al. Novel functions for 2-phenylbenzimindazole-5-suphnicacid: Inhinbition of varian cancer cell resopnses and tumour angiogenesis[J]. JCell Mol Med, 2020, 24(4): 2688-2700.
[21] Pan Huafeng, Zhao Ziming, Shi Yafei, etc. Effects of strengthening the spleen, removing blood stasis and detoxification on inflammatory factors, gastric secretion and motor function in rats with precancerous lesions [C]//Chinese Society of Integrated Traditional Chinese and Western Medicine. Materials of the 13th China Basic Theory Conference on Integrated Traditional Chinese and Western Medicine and the Training Course for Grassroots Doctors in Integrated Management of Traditional Chinese Medicine in County and Townships. Beijing: Chinese Society of Integrated Traditional Chinese and Western Medicine, 2017: 167-169.
[22] Huang Sha, Yang Jianwei, Huang Junshan, et al. Clinical Observation on Xiaozhang Yiliu Fang Combined with Chemotherapy in Treating 35 Cases of Gastric Cancer-induced Malignant Ascites[J]. Journal of Traditional Chinese Medicine, 2017, 58(11): 936-940.
[23] ERIC T U, PEI ZHI CHERYL CHIA, WANJUN CHEN. TGF-βin T cell biology and tumor immunity[J]. Angel or devi, 2014, 25(4): 423-435.
[24] RAMANATHAN S, JAGANNATHAN N. Tumor associated macrophage: A review on the phenotypes, traits and functions[J]. Iran J Cancer Prev, 2014, 7(1): 1-8.
[25] KESKIN S, KUTLUK A C, TAS F. Prognostic and predictive role of angiogenic markers in non-small cell lung cancer[J]. Asian Pac J Cancer Prev, 2019, 20(3): 733-736.
[26] WANG W J, WU Y S, CHEN S, et al. Mushroom β-glucan mayimmunomodulate the tumor-associated macrophages in the lewis lung carcinoma[J]. Biomed Res Int, 2015, 2015: 604385.
[27] PANG L N, HAN S Y, JIAO Y N, et al. Bu Fei Decoction attenuates the tumor associated macrophage stimulated proliferation, migration, invasion and immunosuppression of non-small cell lung cancer, partially via IL-10 and PD-1 regulation[J]. Oncology, 2017, 51(1): 25-38.
[28] KONG F, LI FE, HE Z, et al. Anti-tumor and macrophage activation induced by alkali-extracted polysaccharide from Pleurotus ostreatus[J]. Inter J Biol Macromol, 2014, 69(8): 561-566.
[29] GUO T, YANG Y, GAO M, et al. Lepidium meyenii Walpers polysaccharide and its cationic derivative re-educate tumor-associated macrophages for synergistic tumor immunotherapy[J]. Carbohydr Polym, 2020, 15(250):116904.
[30] SHIGA K, HARA M, NAGASAKI T, et al. Cancer-associated fibroblasts: Their characteristics and their roles in tumor growth[J]. Cancers (Basel), 2015, 7(4): 2443-2458.
[31] KOBAYASHI H, ENOMOTO A, WOODS S L, et al. Cancer associated fibroblasts in gastrointestinal cancer[J]. Nat Rev Gastroenterol Hepatol, 2019, 16(5): 282-295.

[32] WANG Q, QU C, XIE F, et al. Curcumin suppresses epithelialto mesenchymal transition and metastasis of pancreatic cancer cells by inhibiting cancer-associated fibroblasts[J]. Cancer Res, 2017, 7(1): 125-133.
[33] HAN S Y, HU MH, QI G Y, et al. Polysaccharides from polygonatum inhibit the proliferation of prostate cancer-associated fibrolasts cells[J]. Cancer Prev, 2016, 17(8): 3839-3833.
[34] ZHOU B, YU Y, YU L, et al. Sipi soup inhibits cancerassociated fibroblast activation and the inflammatory process by downregulating long noncoding RNA HIPK1AS[J]. Mol Med Rep, 2018, 18(2): 1361-1368.