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Research Progress of the Effect and Mechanism of Active Ingredients of Astragalus Membranaceus on Tumor

Meihuan Fu[1], Xiaofeng Zhai[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
[2]Oncology Department of Traditional Chinese Medicine, The First Affiliated Hospital of Naval Medical University, Shanghai, 200433, China
[*]Corresponding author

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Abstract: Chinese herbal medicine has a long history of treating malignant tumors in China and is considered to be effective in improving the survival. As a traditional Chinese medicine, the immunomodulatory, anti-tumor, anti-inflammatory, anti-aging and anti-hypertensive effects of Astragalus membranaceus have been confirmed by modern pharmacological studies. The main active components of Astragalus membranaceus are astragaloside, astragalus polysaccharide and flavonoids, and all have antitumor effects. The effects of Astragalus membranaceus active substances on tumors by inhibiting tumor proliferation, invasion and metastasis and regulating the immune function of the body are briefly discussed to increase the theoretical understanding of the antitumor effects of Astragalus membranaceus in order to provide reference and help for theoretical ideas in the clinical treatment of its antitumor effects.

1. Introduction

Malignant tumor has been one of the main diseases threatening human health for many years, and the incidence rate has been increasing in recent years, with a high mortality rate, which has caused great pressure on people's physiology and psychology[1]. At present, clinical treatment mainly uses methods such as radiotherapy, chemotherapy, surgical resection, immunotherapy, and targeted therapy. However, due to the high recurrence rate and easy metastasis of malignant tumors to other lesions, the current clinical treatment effect is still not ideal[2]. Therefore, if we want to prolong the survival time of cancer patients and improve their quality of life, we still need to constantly explore new treatment methods and explore new drugs.

Traditional Chinese medicine has a long history in China. It is the treasure of Chinese civilization and the inheritance of ancient Chinese science. In recent years, it has also made great breakthroughs in clinical treatment. Authentic herbs refer to those that have been selected and applied in TCM for a long time, and are produced in specific areas. Compared with the same kind of Chinese herbs produced in other areas, their quality is better and their clinical efficacy is more stable. For example, astragalus membranaceus produced in Shaanxi and other regions is a representative authentic medicinal material. Astragalus membranaceus is a traditional Chinese

medicine, which has many important effects such as improving immune function, lowering blood pressure, promoting body metabolism, improving human heart function, regulating blood sugar, protecting liver and resisting tumor[3]. The main active components of astragalus membranacea are astragaloside, astragalus polysaccharide and flavonoid, and studies have shown that they have antitumor effects[4]. After studying the main active components of astragalus membranaceus, we can proceed to isolate and purify them to study the purity and mechanism of action of more potent antitumor components. This will facilitate the astragalus membranaceus and active ingredients to play a more active role in the diagnosis and treatment of tumor patients.

In this paper, we reviewed and collated the related literatures in recent years, systematically summarized the effective components of astragalus membranaceus and their effects on tumor and mechanism of action, in order to provide theoretical reference and help for its anticancer effect and clinical treatment.

2. Active ingredients of Astragalus membranaceus and its effect on tumors

2.1 Astragalus polysaccharide

Astragalus polysaccharide, as the main active ingredient of astragalus membranaceus, accounts for approximately 32.12 mg/g. It has been isolated into various types, mainly including pectin and heteropolysaccharides[5]. Research has shown that Astragalus polysaccharide has inhibitory effects on many types of tumors and can be used to combat tumors through various pathways such as enhancing the body's immune system, anti-inflammatory, and antiviral effects. The research results of Chan[6]showed that Astragalus polysaccharide can significantly inhibit the proliferation and growth of liver cancer cells, and its inhibitory effect also increases with the increase of concentration, indicating that astragalus polysaccharide can significantly inhibit the growth of tumor cells. In addition, Zhang[7] found that astragalus polysaccharide can inhibit the proliferation and activity of SMMC-7721 cells in mice, and its mechanism of action may be related to its own autophagy. It can be considered that astragalus polysaccharide inhibits tumor growth by inhibiting autophagy of tumor cells. NF-κB is an important transcription factor, which affects tumor cycle and apoptosis, and plays a key role in tumor differentiation, proliferation, apoptosis and metastasis[8]. Studies have confirmed[9]that astragalus polysaccharide can inhibit the proliferation of non-small cell lung cancer cell A549 by down-regulating NF-κB signaling pathway. Administration of NF-κB inhibitor can enhance the inhibition of astragalus polysaccharide on tumor cells, and administration of its agonist can weaken the inhibition of astragalus polysaccharide on tumor. This fully confirms that astragalus polysaccharide is associated with NF-κB. Astragalus polysaccharide can affect tumor proliferation and metastasis by acting on NF-κB. Based on these results, astragalus polysaccharide may inhibit the progression of tumor cells in a variety of ways and play a role in treating cancer patients, with good therapeutic and application prospects.

2.2 Astragaloside

Astragaloside has been shown to have anti-tumor effects. Astragaloside exerts its anti-tumor effect by regulating cell cycle, inducing apoptosis and regulating immunity. Recent studies have shown that astragaloside can inhibit tumor cell proliferation or enhance sensitivity to other drugs. Wang[10]found that the metastasis rate of gastric cancer cells was greatly reduced when treated with different doses of astragaloside. When the concentration of astragaloside increased, the inhibition effect of tumor metastasis was more obvious. At the same time, astragaloside can inhibit the invasion of A549 cells by inhibiting the expression of invasion-related genes MMP-2 and MMP-9, indicating that astragaloside has a good anti-invasion effect. Studies have shown that

astragaloside can enhance the sensitivity of tumor cells to chemotherapy drugs and resist their drug resistance. Astragaloside can improve the sensitivity of prostate cancer to carboplatin by blocking AKT/NF-κ B signaling pathway[11]; and astragaloside can also improve the sensitivity of lung cancer cells to cisplatin by inhibiting endoplasmic reticulum pressure and autophagy[12]. 5-Fluorouracil fights cancer by killing tumor cells and is a commonly used chemotherapy drug for liver cancer. Chen[13] found that the combination of astragaloside II and 5-fluorouracil could cause more damage to tumor cells. astragaloside II could increase the sensitivity of tumor cells to 5-fluorouracil, thus affecting the proliferation and growth of tumor cells. Therefore, astragaloside has certain application prospect in inhibiting tumor invasion and metastasis, inhibiting tumor cell proliferation, preventing cancer and enhancing sensitivity to other drugs, which is worth further exploration.

2.3 Flavonoid

Flavone alone or in combination has a good inhibitory effect on the proliferation and metastasis of tumor cells, mainly composed of compounds such as formononetin; calycosin; ginger, etc. Among them, formononetin and calycosin are the most important tumor suppressants.

Formononetin promotes apoptosis of tumor cells by affecting cell cycle. Park[14] observed the toxic effect and mechanism of formononetin on ovarian cancer ES2 and OV90, and found that formononetin could inhibit the cell cycle of ovarian cancer in G0/G1 phase, thus inducing its apoptosis. At the same time, it was also found that the combination of formononetin and drugs could effectively inhibit the growth and proliferation of two breast cancer cells, thus improving its anticancer activity. Formononetin can also inhibit tumor proliferation and metastasis by regulating tumor microenvironment. By exploring the effect of formononetin on HIF-1α, VEGF and mRNA, the results confirmed that formononetin can inhibit the formation of tumors by inhibiting the expression of HIF-1α and VEGF, thus inhibiting the progression of cervical cancer[15]. Calycosin showed significant inhibitory effect on high incidence of female tumors. Tian[16] showed that calycosin inhibited the growth of estrogen receptor positive breast cancer cells through WDR7 -7-GPR30 feedback loop. In addition, calycosin can significantly increase the tumor suppressor miR-375 of cervical cancer and increase the release of lactate dehydrogenase, while miR-375 gene knockout can significantly reverse its inhibitory effect on cervical cancer[17]. To study the expression of IRE1/XBP1 metabolic pathway related proteins in tumor tissues, it was found that high-dose compounds could significantly reduce the expression of XBP1, IRE1 and GRP78, and increase the expression of CHOP, which indicated that the mechanism of Flavonoid inhibiting tumor growth and immune regulation may involve regulating endoplasmic reticulum through XBP, and Flavonoid can promote apoptosis pathway through endoplasmic reticulum stress and inhibit tumor growth[18].

Therefore, Flavonoid substances in astragalus membranaceus have a good effect on the proliferation and metastasis of tumor cells, and further research on its specific components, mechanism and pathway can increase the possibility of its clinical treatment.

3. Mechanism of action of active ingredients of Astragalus membranaceus on tumors

3.1 Inhibition of tumor cell proliferation

Malignant tumor cells are characterized by unlimited proliferation ability, which is not regulated by the body. Therefore, inducing apoptosis of tumor cells and inhibiting the growth and proliferation of malignant tumor cells are important ways to treat cancer. Active ingredients of Astragalus membranaceus inhibit tumor cell proliferation through different

mechanisms. Autophagy is a double-edged sword in tumorigenesis and development. Under normal circumstances, autophagy can maintain cell homeostasis, eliminate abnormal folded proteins or dysfunctional organelles in tumor cells, and inhibit tumorigenesis. Once tumor is formed, autophagy can promote tumor metabolism and tumor growth by degrading abnormal proteins and organelles in tumor cells. Autophagy of tumor cells creates a nutrient-rich microenvironment for malignant cells and promotes tumor formation[19]. Yang[20] showed that astragalus polysaccharide has a positive effect on inhibiting autophagy of lung cancer A549 cells, which may inhibit autophagy, change tumor microenvironment, make it difficult for tumor cells to adapt to changed pressure environment, and inhibit tumor cell growth and proliferation. Studies have confirmed that [21] astragalus polysaccharide can cause cell cycle arrest and mitochondria dependent apoptosis associated autophagy in HepG2 cells. Its mechanism of action is to promote the transformation of LC3A into LC3B, down-regulate p62 protein, and then induce HepG2 cells to promote autophagy, thus inhibiting the proliferation of tumor cells. In addition, studies have shown that[4] astragalus membranaceus and its active substances also inhibit the proliferation and growth of tumor cells by interfering with the cell cycle of liver cancer and reducing the number of cells in G2/M and S phases. Because cell cycle plays an important role in regulating tumor growth, astragalus membranaceus and its active substances interfere with normal cell cycle, activate apoptosis system and make tumor cells apoptosis, which also affects tumor cell proliferation.

3.2 Inhibition of tumor cell invasion and metastasis

Because early cancer patients do not have obvious clinical manifestations, and there is no early detection in China, most patients are already in the middle and late stages of diagnosis. Studies have shown that invasion and migration of tumor cells are important factors in causing high mortality. Zhang demonstrated [22] that many extracellular proteins bind to specific receptors on the cell membrane, phosphorylate receptor tyrosine and activate STAT3 molecules via tyrosine kinases. These STAT monomers form homo-or heterodimers, which act as transcription factors in the nucleus to regulate the transcription of target genes and promote the spread and metastasis of lung cancer. It has been found that Astragaloside can inhibit JAK/STAT3 signaling pathway in A549 cells, and then inhibit the proliferation and metastasis of A549 cells. Wang[23] found that Astragaloside II may promote the production of Th1 cytokines by activating CD45 pathway, resulting in the activation of Th1 cells, and has anti-metastatic effect on primary liver cancer. Astragaloside regulates protein tyrosine phosphodiesterase CD45 by promoting tyrosine phosphorylation at LCK505, reversing LCK self-inhibition, promoting Th1 cytokine release and T cell activation, thereby mediating its effect on lung metastasis. Cheng[24] found that Astragaloside could inhibit the migration and invasion of ovarian cancer cells SKOV3 to a certain extent, and its mechanism of action was to reduce the expression of MMP2 and MMP9, thus affecting the metastasis and invasion of SKOV3 cells. Tan[25] found that calycosin inhibits the development and metastasis of osteosarcoma by increasing the expression of caspase-3 and decreasing the expression of X-linked apoptosis inhibitor protein, and confirmed that calycosin can inhibit the proliferation and metastasis of tumor by regulating the expression of its related proteins.

3.3 Improvement of immune function

The immune function has the effect of defending against virus invasion and preventing disease invasion. Due to the complex and diverse mechanisms of malignant tumors, the immune function of the body is closely related to the occurrence of tumors. A large number of studies have found that astragalus membranaceus and its active substances can regulate T lymphocytes, T cells, macrophages, and natural killer cells in the tumor immune microenvironment through certain

specific signaling pathways. At the same time, they can regulate the expression levels of certain tumor related cytokines, improve and optimize the tumor immune microenvironment, reverse the immune suppression state of the body, and enhance the immune response ability of tumor patients, Improve the killing ability of tumor cells.

3.3.1 T-lymphocytes

T lymphocytes are not only the main regulatory cells of immune response, but also the executors of immune function. The immune surveillance function performed by T lymphocytes plays a key role in the occurrence and development of tumor prevention in the body[26]. T lymphocytes play a key role in anti-tumor immune response, especially Th1 cell immune response. When Th1 helper cells are activated, cytokines such as IFN-γ and IL-2 are released, triggering an anti-tumor immune response in vivo [27]. Wang[28] found that astragaloside has obvious influence on immune response of Th1 cells in tumor-bearing mice. In tumor-bearing pathological immune environment, astragaloside may make Th1 cells respond by regulating CD45 PTase. Studies have shown that astragaloside has the effect of regulating CD45 PTase, activating nuclear transcription factors and promoting the release of Th1 cytokines, thus improving its immune effect against tumors. Huang[29] found that astragalus polysaccharide can significantly reduce the levels of TGF-β1 and IL-17 in serum. TGF-β1 and IL-17 are thought to promote local inflammation and angiogenesis around tumors, creating a favorable microenvironment for tumor cell growth. These results suggest that decreasing TGF-β1 and IL-17 levels may effectively regulate angiogenesis and inflammation in tumor microenvironment, improve tumor immune microenvironment, and inhibit tumor growth and metastasis.

3.3.2 Regulatory T cells

Regulating T cells (Tregs) essentially has a significant immunosuppressive effect, which can reduce the sensitivity of antigen recognition by affecting antigen-presenting cells (APCs) and dendritic cells (DCs). In addition, it can continuously express glucocorticoid induced TNF receptor family related proteins, directly inhibiting the activity of effector T cells[30]. Therefore, reducing the quantity and expression of Tregs, inhibiting their activity and function, can maintain normal immune function of the body and achieve immune killing effect on tumor cells. Li[31] found that astragalus polysaccharide can block SDF-1 or its receptors through the CXCR4/CXCL12 pathway, thereby inhibiting Treg cell migration and improving the tumor immune microenvironment. Cheng[32] found that astragaloside can downregulate the proportion of Treg cells, restore the normal immune response of T cells, and thereby enhance the anti-tumor immune response. From this, it can be inferred that astragalus membranaceus and its active substances can reduce the number of Treg cells, inhibit their function and activity through certain specific signaling pathways, thereby reversing the immunosuppressive state, restoring the normal immune response ability of T cells, and achieving immune killing effects on tumor cells.

3.3.3 Macrophages

Macrophages are a class of innate immune cells with multifunctional heterogeneity[33]. Tumor-associated macrophages can be polarized into two subtypes, M1 and M2, under the action of different microenvironments and different signaling molecules. M1 type macrophages are mainly involved in anti-infection and anti-tumor immune response process, and have a positive effect on killing external tumor cells; while M2 type macrophages have a certain immunosuppressive effect, so increasing the number of M1 macrophages and decreasing the number of M2 macrophages is the key to improve the phagocytic killing ability of macrophages to tumor cells and inhibit tumor cell

growth and metastasis[34]. Liu[35] found that astragaloside can induce M2 macrophages to polarize to M1 macrophages, improve tumor immune microenvironment, induce apoptosis of colorectal cancer CT26 cells in vitro, inhibit their growth and invasion, reduce the production of anti-inflammatory factors and increase the production of pro-inflammatory factors, so as to exert immune function of macrophages through relevant signaling pathways, and then improve immune function of the body.

In summary, astragalus membranaceus and its active substances can inhibit tumor development by regulating immune cells and improving the tumor immune microenvironment.

4. Conclusion and outlook

Traditional Chinese medicine has a long history in tumor treatment and has a good effect on improving the quality of life of cancer patients. Astragalus membranaceus, as a traditional Chinese herbal medicine, often plays a role in clinical diagnosis and treatment in the form of compound formulas, and has certain therapeutic effects. However, the treatment characteristics of traditional Chinese medicine are multi-faceted, multi-target, and multifaceted, so it is difficult to study its specific mechanism of action. Studies have shown that different active ingredients of Astragalus membranaceus have different effects on tumour cells. Therefore, we need to further analyse and explore the effects of its active ingredients on tumours. At present, the research on its anti-tumor molecular mechanism is more in-depth in the inhibition of cell proliferation, induction of cancer cell apoptosis, and enhancement of immunity by astragalus membranaceus and its active substances. However, the mechanisms in these aspects are very complex and need further exploration.

Overall, active ingredients of Astragalus membranaceus have excellent anti-tumor effects, but scientific theory is still needed to support it. Therefore, studying the anti-tumor active ingredients of astragalus membranaceus at a deeper level has certain reference value for further development and utilization of astragalus membranaceus resources, development of new anti-tumor drugs, and clinical applications.

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