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Mechanism of Response of Astragalus to the Immune System of Lung Cancer

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Abstract: With the acceleration of industrialization and the aging of the population, the incidence and mortality rates of lung cancer are among the highest of all types of cancers, posing a burden to global public health. Currently, lung cancer is treated by various means, including surgery, radiotherapy, chemotherapy, and so on, but it still faces many challenges, such as chemotherapy resistance and bone marrow suppression. As a traditional qi tonic herb, Astragalus has shown extensive pharmacological activity in antitumor therapy. This article describes the active components and anti-tumor mechanism of Astragalus from multiple perspectives, including regulating the ratio of $CD4^+/CD8^+$ T cells, promoting B-cell proliferation and differentiation, promoting the synthesis and release of TNF-α, promoting the secretion of immune-enhancing factors, such as interleukin-2, scavenging excessive ROS in lung cancer cells and the body, and maintaining the oxidative-antioxidative balance. It also promotes the synthesis and release of TNFα, the secretion of interleukin-2 and other immune-enhancing factors, the removal of excessive ROS from lung cancer cells and the organism, the maintenance of oxidative-antioxidative balance, etc., which reduces postoperative complications and adverse reactions, and provides a new way of thinking and a theoretical framework for the clinical treatment of lung cancer.

Keywords: Regulation of immune mechanisms, Oxidative stress, Lung cancer, Astragalus

1. Introduction

Globally, lung cancer is the primary cause of cancer-related fatalities. In addition, lung cancer is associated with the highest mortality among all cancer types [1]. According to relevant data, lung cancer ranks first in the incidence rate and mortality rate of cancer in China. In 2022, there will be about 4,824,700 new cancer cases in China, among which lung cancer is the first cause of incidence, and lung cancer also ranks first in the death of cancer cases, and its high cost of treatment creates a psychological and practical burden for patients and their families. In the current treatment of lung cancer by Western medicine, it has big side effects and is easy to produce drug resistance, while Chinese medicine treatment has a better prospect. Chinese medicine treats lung cancer from a holistic point of view, with less side effects, among which, Astragalus has certain advantages in the treatment of lung cancer. According to Chinese medicine, a deficiency of positive qi is the root cause of tumor occurrence and development [2]. As a traditional medicinal material for invigorating qi, Astragalus membranaceus has multiple effects, such as raising yang to lift depression, benefiting Wei to consolidate exterior, and supporting toxin to promote granulation, etc. Its application in anti-tumor therapy has shown extensive pharmacological activities [3]. Various components of Astragalus have

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been proved to have the effects of anti-radiation damage, enhancement of cellular immune function, and at the same time can reduce the side effects of patients after radiotherapy treatment, as well as prolong the life of patients and improve the quality of life [4]. Currently, there is no specific analysis on the application of the response mechanism of Astragalus to the immune system of lung cancer, this paper aims to explore the study of the response mechanism of Astragalus to the immune system of lung cancer, comprehensively analyze its immune regulation mechanism, oxidative stress, etc., to provide a new way of thinking for the treatment of lung cancer, and to promote the development of the combined treatment of traditional Chinese and Western medicine.

2. Mechanisms to lung cancer

The development of lung cancer is a complex process, it involves many mechanisms such as immune cells, inflammatory factors, and oxidative stress [5].

Abnormal immune cell function: The ratio of $CD4^+/CD8^+$ T cells is imbalanced, and cytokines secreted by lung cancer cells can inhibit the differentiation of $CD4^+$ T cells to helper T cell 1 (Th1) cells and promote their differentiation to regulatory T cells. In lung cancer patients, the $CD4^+$T cell helper function is weakened, affecting the activation of $CD8^+$T cells; the cytotoxicity of $CD8^+$T cells is reduced, and the ability of $CD8^+$T cells to kill tumor cells is weakened. B cell activation and proliferation function are reduced and interfere with normal differentiation. In lung cancer patients, B cells may produce some antibodies against tumor-associated antigens due to the complexity and heterogeneity of tumor antigens. Still, these antibodies often cannot effectively clear tumor cells and may even promote the growth and metastasis of tumor cells—reduced killing activity of NK cells and inhibition of NK cell proliferation. In lung cancer patients, the number of NK cells may decrease, the expression of activation receptors on their surface decreases, and the expression of inhibitory receptors increases, leading to a decrease in the ability of NK cells to recognize and kill tumor cells.

Abnormal expression of inflammatory factor levels: the synthesis and release of TNF - α (tumor necrosis factor - α) is inhibited, TNF - α can induce tumor cells to Generate various cytokines and chemokines, thereby amplifying the inflammatory response, tumor cell migration and invasion are promoted by certain factors. These factors also render tumor cells more resistant to chemotherapeutic drugs. As a consequence, there is a spike in inflammation levels throughout the body, which leads to damage in tissue cells.IL-6 (interleukin-6) secretion is increased and the ratio of Th1/Th2 cells is imbalanced. In lung cancer patients, cancer cells may secrete IL-6, which may activate the JAK-STAT3 signaling pathway, promote the proliferation of lung cancer cells, inhibit apoptosis, and induce the production of acute phase proteins involved in inflammatory responses and lead to inflammation-related symptoms. Increased secretion of IL-1β, a precursor to IL-1β, and the activation of the NLRP3 inflammatory vesicle in lung cancer-related inflammation. The NLRP3 inflammatory niche is easily activated in lung cancer-associated inflammation, prompting the cleavage of IL-1β precursors and the release of mature IL-1β, which triggers the early initiation and amplification of inflammation, leading to increased lung tissue damage.

Oxidative stress abnormalities: oxidative stress is one of the important pathogenic factors of lung cancer, which refers to the imbalance between oxidation products and antioxidant defense mechanisms in the body [6]. With the progression of lung cancer, SOD activity tends to decrease and is unable to effectively scavenge the continuously generated ROS, leading to a dysregulation of the oxidation and antioxidant balance, and excessive ROS attack intracellular biomolecules, factors play multiple negative roles, promoting the proliferation, facilitating invasion and enabling metastasis of lung cancer cells, among others. Metabolic changes in tumor cells may cause GSH - Px synthesis to be inhibited or activity to be reduced, on the other hand, the continuous oxidative stress state makes GSH-Px consumption increase, which makes the cell's scavenging ability of peroxides such as

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hydrogen peroxide decrease, and the accumulation of peroxides in the cell further triggers oxidative damage and promotes the development of lung cancer.

3. Immunomodulatory mechanisms of astragalus on lung cancer

3.1. Effects on immune cells

3.1.1. Regulation of the ratio of $CD4^+/CD8^+$ T cells

T cells will inhibit the body's immune response and down-regulate the expression of their own MHC-class I molecules, making it difficult for $CD8^+$ T cells to recognize tumor antigens, and the immunosuppressive factors released by lung cancer cells will inhibit the activation and proliferation of $CD8^+$ T cells, so that their ability to kill lung cancer cells is weakened. Astragalus helps maintain immune homeostasis by adjusting the $CD4^+/CD8^+$ T-cell ratio to normal levels. When the body's immune function is disordered, Astragalus can restore the immune balance by adjusting this ratio. In some immunocompromised animal models, for example, in the experiments of Astragalus injection combined with sensitized dendritic cells for the treatment of lung cancer mice, the ratio of $CD4^+$T and $CD8^+$T cells in the splenocytes of the mice was significantly elevated, as well as the ratio of IL - 2/IL - 4 in the combined treatment group, which has a significant in vivo inhibition of the metastatic effect of lung cancer. It was concluded that after using Astragalus, an increase in $CD4^+$ T-cell numbers was observed, whereas $CD8^+$ T-cell levels showed little change, the $CD4^+/CD8^+$ ratio was elevated, and the immune function was improved.

In addition, lung cancer cells will escape the immune surveillance of T lymphocytes through multiple mechanisms, and they will inhibit the activity of T lymphocytes, resulting in the tumor cells being able to escape the attack of T lymphocytes and be able to proliferate and metastasize in vivo, whereas the active ingredients in Astragalus can promote the proliferation of T lymphocytes, increase their number, and enhance the cellular immune function of the organism. For example, in in vitro experiments, Astragalus polysaccharides significantly enhance T cell proliferation and augment their functional activity.

3.1.2. Promote B-cell proliferation and differentiation

Lung cancer cells will release cytokines such as TGF -β, IL -10, etc., which inhibit the activation, proliferation, and antibody secretion of B-lymphocytes so that B-lymphocytes cannot effectively produce specific antibodies against lung cancer cells, experimental evidence indicates astragalus mitigates lung cancer-mediated humoral immunosuppression, with observed enhancements in B cell expansion and activation markers. Through the upregulation of co-stimulatory molecules on B cells, astragalus polysaccharides facilitate intercellular crosstalk between B lymphocytes, T lymphocytes and other immune cells, thereby potentiating B cell activation and antibody secretion.

Lung cancer cells may also interfere with the normal differentiation process of B lymphocytes. Under the influence of the lung cancer microenvironment, B lymphocytes may differentiate into abnormal cell subpopulations, such as regulatory B cells (Breg). Breg cells may inhibit the function of other immune cells by secreting inhibitory cytokines and promoting the immune escape of tumor cells. Astragalus can inhibit lung cancer microenvironment-induced differentiation of B lymphocytes to abnormal subpopulations, such as Breg cells, and enhance the body's anti-tumor humoral immune response by regulating the intracellular signaling pathway so that the B lymphocytes can maintain the normal differentiation and functional state.

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3.1.3. Increase the killing activity and number of NK cells

Lung cancer cells express multiple immunosuppressive molecules, including programmed death ligand-1 (PD-L1), that engage with cognate receptors on NK cells to suppress their cytotoxic function, making it difficult to effectively recognize and kill lung cancer cells. In addition, cytokines such as TGF -β and IL -10 secreted by lung cancer cells also inhibit the function of NK cells and reduce their cytotoxicity. Astragalus can increase the killing activity of NK cells so that they can recognize and kill tumor cells, virus-infected cells, and other abnormal cells more effectively. Moreover, the active ingredients in Astragalus can activate the signaling pathway of NK cells, Astragalus polysaccharides stimulate cytotoxic granule release and potentiate NK cell-mediated cytotoxicity against lung cancer cells.

The immunosuppressive microenvironment created by lung cancer cells will inhibit the proliferation of NK cells, and these inhibitory cytokines will interfere with the normal metabolism and signaling pathway of NK cells, so that the proliferation ability of NK cells will be decreased and the number will be reduced, thus weakening the anti-tumor immune response of the body. Astragalus can improve the inhibitory effect of the lung cancer microenvironment on NK cells and promote the proliferation of NK cells. Studies have shown that astragalus polysaccharides can stimulate NK cells to secrete cytokines such as IL-2, which in turn can promote the proliferation and activation of NK cells, forming a positive feedback regulation, through NK cell population expansion, astragalus polysaccharides potentiate systemic anti-tumor immunity.

3.2. Effects on inflammation-related factors

3.2.1. Promotion of TNF-α synthesis and release

In the early stages of lung cancer, the body's immune system will recognize tumor cells and initiate an immune response. Immune cells such as macrophages will be recruited into the tumor microenvironment and release inflammatory factors such as TNF-α in an attempt to kill tumor cells, at which time the level of TNF-α will be elevated. As the tumor develops, Lung cancer cells will release a variety of immunosuppressive factors, such as TGF -β (transforming growth factor β), IL -10, etc., which will inhibit the function of immune cells, such as macrophages, and reduce the secretion of TNF-α. Meanwhile, Lung cancer cells potentially suppress TNF-α production by triggering immune cell apoptosis, thereby inhibiting the host's anti-tumor immune response [7]. Astragalus may promote the function of immune cells, such as macrophages, and enhance their phagocytosis and antigen-presenting ability, thus inducing macrophages to secrete more TNF -α [8]. Studies have shown that astragalus polysaccharides can activate signaling pathways in macrophages, promote the transcription and translation of the TNF -α gene, increase the synthesis and release of TNF -α, and enhance the anti-tumor immune response of the body.

3.2.2. Inhibition of IL-6 signaling and secretion

Binding of IL-6 to its receptor activates the JAK/STAT signaling pathway. In lung cancer cells, sustained activation of this signaling pathway promotes the expression of genes related to cell proliferation, survival, and angiogenesis, such as c-Myc and Bcl-2, thereby promoting the development of lung cancer. The activated JAK/STAT signaling pathway impairs immune cell activity, thereby enabling lung cancer cells to circumvent host immune surveillance. Astragalus can regulate the JAK/STAT signaling pathway, inhibit the signaling of IL-6 after binding to its receptor, and reduce related gene expression and protein synthesis. It can also normalize the imbalanced Th1/Th2 cell ratio and reduce IL-6 secretion by helper T cells through overall immune regulation, which in turn reduces the inflammatory response and alleviates inflammation-related symptoms [9].

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Experimental data demonstrate that astragaloside suppresses IL-6 production in A549 cells, as evidenced by decreased IL-6 levels in conditioned media.

3.2.3. Inhibition of IL-1β secretion and reduction of release

Lung cancer cells release several danger-signaling molecules that can be recognized by pattern recognition receptors on the surface of immune cells such as macrophages. Among them, NLRP3 (NOD-like receptor protein 3-containing) inflammatory vesicles are one of the important receptors that recognize these signals. Astragalus inhibits the assembly and activation of NLRP3 inflammatory vesicles and reduces the cleavage and maturation release of IL-1β precursors. Meanwhile, it regulates intracellular calcium ion concentration and so on, affecting the IL-1β secretion process, alleviating the early initiation and amplification of inflammation, and reducing the tissue damage caused by inflammation. The study showed that by establishing an acute lung injury rat model, it was found that after the intervention of giving Astragalus injection, IL-1β expression in rat lung tissue was significantly downregulated, and the pathological damage of the lung tissue was also alleviated, which proved that Astragalus could inhibit IL-1β secretion to reduce lung inflammation [10].

4. Oxidative stress in lung cancer by Astragalus

4.1. Free radical scavenging capacity

Oxidative stress serves as a critical regulator of multiple physiological processes, including apoptosis, cell survival, and proliferation [11]. Increased free radicals in lung cancer patients attack cellular lipids, proteins, and DNA, leading to cellular damage and abnormal function. For example, free radicals can attack cellular DNA, leading to DNA strand breaks, base modifications, and other damage. For example, hydroxyl radicals (-OH) can directly react with deoxyribose and bases in DNA molecules, causing damage to the DNA structure. Elevated levels of the DNA damage biomarker 8-hydroxy-2'-deoxyguanosine (8-OHdG) are observed in lung cancer tissues compared to normal adjacent tissues, which indicates that excessive free radicals can cause DNA damage in lung cancer cells, which in turn may lead to gene mutation and promote the proliferation and malignant transformation of tumor cells. The active components of Astragalus membranaceus include Astragaloside (AMS), Astragalus polysaccharide (APS) and Astragalus flavone (AFS), which have antioxidant properties and can directly scavenge free radicals, notably the oxygen-derived free radicals: superoxide anion (O_2^-) and hydroxyl radical (·OH), reduce the content of lipid peroxidation products such as malondialdehyde, protect cell structure and function, and reduce damage to normal tissue cells due to oxidative stress [12-15]. Excessive free radicals inhibit immune cell activity and affect the secretion of immune factors. Scavenging free radicals by Astragalus can restore the function of immune cells such as T lymphocytes and NK cells, promote the secretion of immune-enhancing factors such as interleukin-2, enhance the body's immune function, and enhance the ability to recognize and kill lung cancer cells.

Astragalus is generally used as an adjunct to the comprehensive treatment of lung cancer. During surgery, radiotherapy, and chemotherapy, the use of astragalus can reduce treatment-induced oxidative stress and immunosuppression. For example, postoperative administration of Astragalus extract or herbal compound containing Astragalus in lung cancer patients can accelerate physical recovery, reduce complications such as infection, lung atelectasis, and pleural effusion, and improve patients' tolerance and compliance to radiotherapy. Some studies have shown that the incidence of infection can be reduced from about 30% to about 15% with conventional treatment by taking a Chinese medicine compound containing Astragalus after lung cancer surgery. As for lung cancer patients with complications of lung atelectasis and pleural effusion, the incidence of lung atelectasis was reduced from about 10% to less than 5% and the amount of pleural effusion was also reduced

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after the adjuvant treatment with Astragalus extract. Used during radiotherapy, it can reduce gastrointestinal and myelosuppression adverse reactions. Clinical observation found that the severity of gastrointestinal reactions was significantly reduced in patients using Astragalus extract, and the incidence of severe nausea and vomiting was reduced from 30% - 40% to 15% - 20%, and the patients' eating situation and quality of life were improved. As for lung cancer patients with myelosuppression during radiotherapy, the incidence of leukopenia decreased from about 70% in radiotherapy alone to 40%-50%, and the incidence of thrombocytopenia was also reduced in patients taking Astragalus Traditional Chinese Medicine Compound.

4.2. Regulation of antioxidant enzyme activities

In lung cancer patients, the rapid proliferation and metabolism of lung cancer cells generate a large amount of reactive oxygen species (ROS), such as superoxide anion radicals and hydroxyl radicals. These excessive ROS will break the oxidative-antioxidative balance of the body and damage cellular biomolecules, such as DNA, proteins, and lipids, which in turn promote the proliferation, invasion, and metastasis of lung cancer cells. At the same time, lung cancer cells also inhibit the activity of antioxidant enzymes so that the body's ability to remove ROS decreases. While Astragalus can enhance the activity of antioxidant enzymes, studies have shown that astragalus polysaccharide can activate the Nrf2/ARE signaling pathway in lung cancer cells, prompting the translocation of Nrf2 protein from the cytoplasm to the nucleus to bind to the antioxidant response element (ARE), which in turn up-regulates the expression of genes for antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GSH - Px) and Catalase (CAT), etc., which can effectively scavenge excessive ROS in lung cancer cells and the organism, maintain the oxidative - antioxidant balance, and alleviate oxidative stress injury, thereby suppressing the growth, proliferation and metastatic potential of lung cancer cells, and ultimately inhibiting lung cancer progression.

5. Conclusion

As an immunomodulator, Astragalus, its main active ingredients, saponins, flavonoids, and polysaccharides, can effectively regulate immune function and prevent tumors. Many components in Astragalus have been proved to exert anti-lung cancer effects through multiple pathways, such as regulating the ratio of $CD4^+/CD8^+$ T cells, promoting the proliferation and differentiation of B cells, promoting the synthesis and release of TNF-α, inhibiting the signaling and secretion of IL-6, promoting the secretion of immune-enhancing factors such as interleukin-2, and maintaining the immunity of lung cancer cells and excessive ROS in the body. secretion, scavenging excessive ROS in lung cancer cells and the body, maintaining the oxidative-antioxidative balance, etc, these results offer promising translational opportunities for developing innovative lung cancer interventions.

However, there are still some deficiencies: Firstly, the anti-neoplastic activity of Astragalus, mediated by its various active constituents, involves complex multi-target interactions and signaling pathways that require further elucidation. Secondly, the different physique, condition, and medication regimen of patients may lead to individual differences in the efficacy of Astragalus, and further studies are needed to clarify its influencing factors. The majority of current investigations have been conducted using in vitro systems or animal models and the numbers of clinical studies are limited and the sample size is small, and the design is not rigorous enough, making it difficult to comprehensively assess the efficacy and safety of Astragalus.

Future research direction: Modern technology can be utilized to study in depth the mechanism of action of Astragalus and its active ingredients and to clarify its specific targets and pathways for regulating the immune system. In addition, large-sample, multi-center clinical trials will be conducted to evaluate the efficacy and safety of Astragalus alone or in combination with other therapies in the

treatment of lung cancer. Finally, the clinician will study the individual differences in the efficacy of Astragalus and explore the individualized drug regimen based on patients' genes and immune status.

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