

Correlation between “Qing Fei San Jie Wan” and key gene CTLA-4 in lung cancer

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Abstract: Lung cancer is the most threatening malignant tumor to the health and life of the population. In the past fifty years, the incidence and mortality of lung cancer have increased significantly, and Chinese residents are facing a serious burden of lung cancer. The co-inhibitory molecule CTLA-4 on the surface of T cells is a glycoprotein expressed on the surface of active CD4 and CD8 positive T cells, which transmits inhibitory signals to T cells, has the effect of down-regulating or terminating T cell activation, and participates in Negative regulation of the immune system. “QingFeiSanJieWan” has the effect of enhancing the function and effect of the immune system, which is of great significance to the human body's fight against lung cancer, and has a certain promoting effect on the activation of T cells and other lymphocytes. The drug has different inhibitory effects on the expression of co-inhibitory molecule CTLA-4 on the surface of CD4+ and CD8+ T cells. Preventing CTLA-4 and then inhibiting the immune response effect of T cells, thereby enhancing the immune function, fighting against lung cancer cell antigens in the body, and providing new immunological ideas for the treatment and drug mechanism of lung cancer. Using “QingFeiSanJieWan” to treat CTLA The anti-resistance effect of -4 proves that the drug is of great significance to the therapeutic mechanism of lung cancer.

Keywords: “QingFeiSanJieWan”, CTLA-4, lung cancer gene, immune response

1. Current status of lung cancer research

Lung cancer is the malignant tumor with the highest morbidity and the fastest-growing mortality among cancers, and the greatest threat to the health and life of the population. It poses a great threat to human beings. Over the past fifty years, many countries have reported that the morbidity and mortality of lung cancer have increased significantly, making the morbidity and mortality of lung cancer account for the first place among all malignant tumors in the world. Lung cancer has become the malignant tumor with the highest number of deaths, morbidity and mortality in China, and it has an increasing trend year by year [1]. The age-standardized 5-year survival rate of lung cancer patients is only 16.1% [2], and Chinese residents are facing a serious burden of lung cancer, as shown in Table 1.

Table 1: Ranking of the top 10 cancers among men and women in China in 2015^[3]

Ranking	Number of cases of men and women (10,000, proportion)	Number of deaths of men and women (10,000, proportion)
1	Lung cancer(73.33,17.09%)	Lung cancer(61.02,21.68%)
2	Gastric cancer(67.91,15.82%)	Gastric cancer(49.80,17.70%)
3	Esophageal cancer(47.79,11.14%)	Liver cancer(42.21,15.00%)
4	Liver cancer (46.61,10.86%)	Esophageal cancer(37.50,13.33%)
5	Colorectal cancer(37.63,8.77%)	Colorectal cancer(19.10,6.79%)
6	Breast cancer(27.24,6.35%)	Pancreatic cancer(7.94,2.82%)
7	Brain and CNS tumors(10.1,2.35%)	Breast cancer(7.07,2.51%)
8	Cervical cancer(9.89,2.3%)	Brain and CNS tumors(6.10,2.17%)
9	Pancreatic cancer(9.01,2.10%)	Leukemia(5.34,1.90%)
10	Thyroid cancer(9.00,2.1%)	Lymphoma(5.21,1.85%)

2. Immune response and CTLA-4

2.1 T cells and lung cancer

In the human body, a series of responses of the immune system have a positive effect on the body's fight against lung cancer. Among them, the immune response involving T cells can well target the proliferation and spread of lung cancer cells. The surface of T cells has a variety of surface molecules, each of which can exert different functions, regulate the activity of T cells, and have different effects on the immune system such as inhibition and regulation. In addition, the cellular immune process in which T cells participate is an important means for the human immune system to deal with lung cancer tumor cells [4].

2.2 Immune checkpoint

Immune checkpoints, as regulators of the immune system, are critical for maintaining autoimmune tolerance and regulating the duration and extent of immune responses in peripheral tissues. However, these pathways can be "hijacked" by tumors and continuously activated, inhibiting anti-tumor immunity and promoting tumorigenesis[5]. There are two types of checkpoint molecules associated with immune regulation, stimulatory checkpoint molecules and inhibitory checkpoint molecules. Inhibitory checkpoint molecules are targets of cancer immunotherapy with potential use in many types of cancer. The theory of immunoediting expounds the complex relationship between cancer and the immune system. The theory of immunoediting is a dynamic process of mutual balance between host and object, which consists of three stages: elimination, balance and escape. During the elimination phase, the development of abnormal cells induces potent innate and acquired responses leading to tumor killing[6]. Negative co-stimulatory signals elicited by the programmed cell death 1 (PD-1) receptor (Fig.1) lead to a decline in the T cell receptor (TCR), which is involved in mechanisms of immune tolerance and immune response limitation[7]. Therefore, several monoclonal antibodies (mAbs) targeting immune checkpoints (ICIs) have been reported successively and serve as fundamentals of care strategies for patients with advanced non-small cell lung cancer.

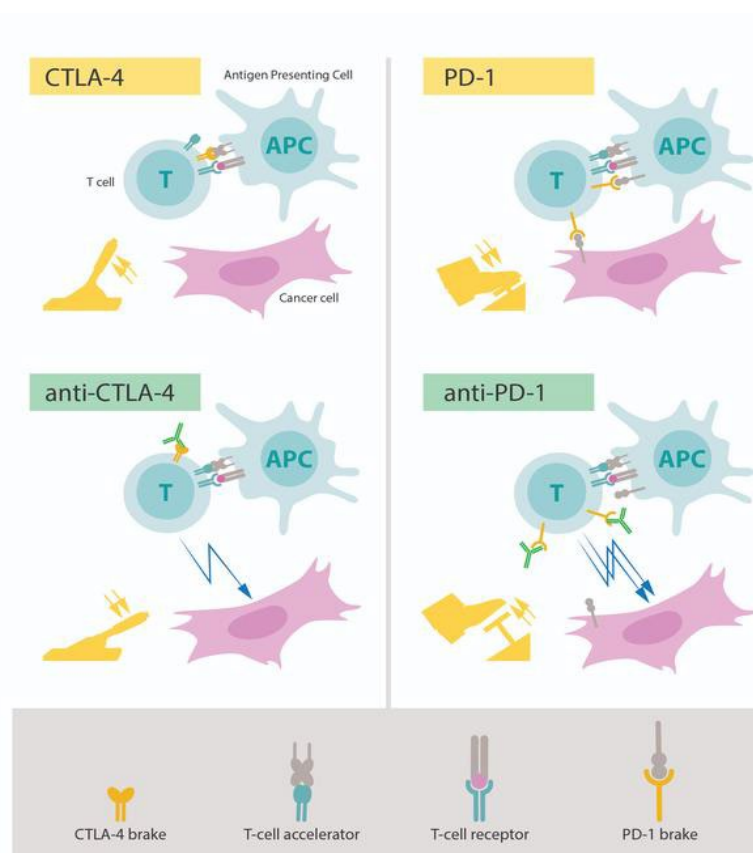


Figure 1: CTLA-4 antibody and PD-1 antibody

2.3 CTLA-4 immune mechanism

The co-inhibitory molecule CTLA-4 (also known as CD152) on the surface of T cells is a glycoprotein expressed on the surface of active CD4 and CD8 positive T cells, which transmits inhibitory signals to T cells, has the effect of down-regulating or terminating T cell activation, and participates in Negative regulation of the immune system. James P. Allison's team found that CTLA-4 antibodies can prevent its expression, thereby preventing the negative regulation of T cells, releasing the "brake" of T cells, thereby activating the immune system to attack cancer cells^[8]. The mechanism by which CTLA-4 inhibits T cells may be to inhibit the production of cytokine IL-2 (interleukin 2). CTLA-4 inhibits the accumulation of IL-2 mRNA induced by CD3/CD28 (co-stimulatory molecule) and inhibits the transcription of IL-2 by reducing the accumulation of NF-AT (nuclear factor of activated T cells) in the nucleus. After T cells are fully activated, without the participation of IL-2, activated T cells cannot proliferate and differentiate, which will lead to apoptosis after T cell activation with a high probability. By inhibiting the expression of CTLA-4 to prevent this process, the number of CD4+ and CD8+ T cells in the body will increase, and the cytotoxic effect will be enhanced, thereby killing lung cancer cells in the body, and finally can produce a therapeutic effect on lung cancer^[9].

3. "QingFeiSanJieWan" and lung cancer

3.1 Research Progress of "QingFeiSanJieWan"

"QingFeiSanJieWan" (formerly known as Shenling Pills) is a specialized medicine for the treatment of respiratory tract tumors. Gynostemma Gynostemma Extract, Panax notoginseng, Bitter Scrophulariaceae Extract, Chuan Fritillaria, Ginkgo, Pinellia, Ganoderma lucidum, Cordyceps sinensis, pearls, donkey-hide gelatin, and artificial bezoar are processed and processed. It has the effects of clearing the lungs and dispelling stagnation, promoting blood circulation and relieving pain, detoxifying and reducing phlegm, and has a great effect on improving lung function and promoting normal cell proliferation and metabolism in the lungs. The frequency of clinical use of Qingfei Sanjie Pills is gradually increasing at home and abroad, and many clinical data can provide a feasible basis for its treatment of lung cancer.

3.2 Lung cancer treatment methods

Currently, the main treatment methods for lung cancer are radiotherapy, chemotherapy, and surgery, but radiotherapy and chemotherapy have serious side effects, and surgery is difficult and has high risks^[10]. Traditional Chinese medicine and modern medicine in our country are blended with each other, and many Chinese patent medicines with outstanding effects have been produced. Western medicine treats the symptoms, and Chinese medicine treats the root cause has always been deeply rooted in the hearts of the people. Therefore, "QingFeiSanJieWan", which are used to treat lung cancer, are favored by researchers. Qingfei Sanjie Pill has the functions of clearing lung and resolving stagnation, promoting blood circulation and relieving pain, detoxifying and reducing phlegm, and has a great effect on improving lung function and promoting normal cell proliferation and metabolism in the lung.

3.3 The relationship between "QingFeiSanJieWan" and CTLA4

Studies have shown that a variety of ingredients have an antagonistic inhibitory effect on CTLA-4, for example, a certain dose of Gynostemma polysaccharide (GPG) can significantly improve the activity of NK cells, and also improve the transformation ability of lymphocytes^[11]. Ginkgo albumin (GAP) can promote the proliferation of activated and unactivated T and B lymphocytes, enhance the cytotoxicity of NK cells and stimulate the secretion of IL-2 in splenic lymphocytes^[12]. Experiments have shown that Cordyceps can induce mouse spleen B lymphocytes to express higher levels of IL-2 receptors, amplify and regulate the immune response of B lymphocytes^[13]. Pearl powder can increase the number and function of T and B lymphocytes^[14]. The inhibitory effect of CTLA-4 increases the number of CD4+ and CD8+ in the body, which exhibits certain promoting effect on the activation and proliferation of T cells. Inhibit expression on the surface of T cells, thereby promoting the further activation and differentiation of T cells into cytotoxic T, exerting its cytotoxic effect on target lung cancer cells. At the same time, the changes in the number of CD4+ and CD8+ in peripheral blood in vivo may indicate that the medicine can inhibit CTLA-4 to expand the immune effect and achieve a therapeutic effect on lung cancer^[15].

4. Conclusion

Therefore, discussions of the Strategy on “QingFeiSanJieWan” in Treating Lung Cancer become more. “QingFeiSanJieWan” can enhance the function and effect of the immune system, which is of great significance to the human body's fight against lung cancer, and has a certain promotion effect on the activation of lymphocytes such as T cells. The main components of “QingFeiSanJieWan” have different inhibitory effects on the expression of the co-inhibitory molecule CTLA-4 on the surface of CD4⁺ and CD8⁺ T cells, and inhibit the immune response produced by cytotoxic T cells by preventing the expression of CTLA-4. Therefore, “QingFeiSanJieWan” can promote proliferation and activation, enhance immune function, fight against lung cancer cell antigens in the body, and provide new immunological ideas for the mechanism of drug treatment of lung cancer.

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