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Discussion on the Effect of Small Qinglong Decoction on Airway Remodeling in Asthma, Based on TGF-β1/Smads Signaling Pathway and MMP-9

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Abstract: ***Airway remodeling has always existed in the process of bronchial asthma, Airway remodeling is a key pathological change in the development of bronchial asthma, It is one of the important factors of recurrent and refractory. In this paper, TGF-β1 / smads signaling pathway and MMP-9 were used to explore the effect of Small qinglong decoction on airway remodeling in asthma. TGF-β1 / smads signaling pathway, it is the main regulatory factor leading to airway remodeling in bronchial asthma, by activating the Smad2 / 3 pathway, stimulate the proliferation of fibroblasts into myofibroblasts, resynthesized collagen and fibronectin accumulate and deposit in the extracellular matrix (ECM), eventually leading to airway remodeling. Matrix metalloproteinase-9 (MMP-9) is a key enzyme in ECM remodeling, it can degrade various protein components of ECM, involved in the occurrence of airway remodeling. TGF-β1 can induce neutrophils to release a large amount of MMP-9, exacerbating airway remodeling by promoting the synthesis of ECM. Small qinglong decoction is widely used in bronchial asthma clinical treatment. It can inhibit the expression of TGF-β1/smads signaling pathway, reduces MMP-9 secretion, reduces inflammatory reaction, then affect the airway remodeling of bronchial asthma.***

Keywords: Bronchial asthma, Airway remodeling, Small qinglong decoction, TGF-β1/smads signaling pathway, MMP-9**.**

1. Current Status of Bronchial Asthma

Bronchial asthma (BA) is a common respiratory allergic inflammatory disease. Its morbidity and mortality have an increasing trend year by year. Modern medicine believes that bronchial asthma is a chronic inflammatory disease of the respiratory tract involving a variety of cells such as eosinophils, mast cells, lymphocytes and neutrophils, respiratory epithelial cells, and cellular components. It is characterized by chronic eosinophilic airway inflammation, airway hyperresponsiveness and irreversible airway remodeling. The change of airway structure caused by repeated episodes of symptoms is called airway remodeling [1]. Airway epithelium is both a mediator and a target of inflammation in asthma, remodeling and blocking are shown in its downstream effects. Airway remodeling is another major pathological feature of asthma. Structural changes associated with asthma include impaired epithelial integrity, subepithelial fibrosis, goblet cell hyperplasia / metaplasia, smooth muscle hypertrophy / hyperplasia, and vascular enhancement. Airway remodeling can lead to persistent airway stenosis, airway hyperresponsiveness and decreased lung function, which is the main reason why asthma is difficult to cure [2]. Studies have shown that airway inflammation can promote airway remodeling, and airway remodeling has continued to exist in the course of asthma, eliminating inflammation does not prevent the progression of airway remodeling, nor can it delay disease progression, airway remodeling is closely related to the severity of the disease. Therefore, inhibiting airway remodeling is of great significance for improving lung function and quality of life in patients with asthma. At present, there is no breakthrough in the treatment of airway remodeling, which seriously restricts the long-term control of asthma patients [3]. The incidence of asthma is affected by many factors, western medicine treatment of asthma mainly includes glucocorticoids, bronchodilators, leukotriene modulators, biological agents, etc, it has great advantages in relieving acute attack of asthma, can quickly control the disease, however, long-term use has problems such as large side effects, dependence, and inability to cure. ought to choose more reasonable and effective treatment options [4]. In recent years, traditional Chinese medicine has unique advantages in the prevention and treatment of airway remodeling in asthma. Whether it is a compound of traditional Chinese medicine or a single drug or monomer, it is conducive to the intervention of airway remodeling and has irreplaceable advantages of Western medicine [5, 6,7].

2. Research Progress of Traditional Chinese and Western Medicine

2.1 The Understanding and Research Progress of BA in Modern Medicine

Bronchial asthma is a common chronic non-communicable disease in children. The main clinical manifestations are recurrent shortness of breath, chest tightness and cough. Respiratory inflammation, airway hyperresponsiveness and airway remodeling are the main pathological features of asthma. Airway remodeling refers to the pathological changes in the normal structure of the airway, including the changes in the structure of the airway itself and the changes in the structure, composition and function of the airway wall cells. The structural changes caused by this complex multi-cellular process include epithelial cell damage and repair, epithelial mesenchymal transformation, subepithelial fibrosis, extracellular matrix precipitation (ECM), airway smooth

muscle cell (ASMC) proliferation and migration, and airway wall angiogenesis. The process and degree of airway remodeling vary in individual patients depending on the course and severity of the disease [5]. At present, it is generally believed that asthma is a high T2 inflammatory phenotype asthma.Th2 cells play an important role in promoting airway smooth muscle proliferation and mucus secretion by releasing a variety of cytokines, such as interleukin 4 (IL-4), which can induce eosinophil (EOS) activation and assist B cells to produce IgE, thereby regulating airway inflammation, overexpression of Th2 cytokines can promote airway remodeling in asthma. In asthma with low T2 inflammatory phenotype, the Th1 / Th17 inflammatory pathway is imbalanced. Th17 cells secrete IL-17, stimulate the production of fibrogenic cytokines such as tumor necrosis factor-α, promote the proliferation and deposition of fibroblasts, myofibroblasts and smooth muscle cells, and then prolong airway remodeling [8].

TGF-β1 is one of the strongest pro-fibrotic factors known to date. At present, a large number of studies have shown that TGF-β1 / Smad signaling pathway is closely related to airway remodeling in bronchial asthma, which is the main regulatory factor leading to airway remodeling in bronchial asthma. TGF-β1 can promote the proliferation of airway smooth muscle cells and fibroblasts, cause subbronchial thickening and collagen deposition, and ultimately lead to bronchial stenosis in patients with bronchial asthma. If antigen stimulation causes chronic airway inflammation again, it will lead to excessive increase of TGF-β1, resulting in tissue fibrosis and chronic airway obstruction and airway reconstruction [9]. Smad protein is a specific intracellular signal transduction protein of TGF-β/Smads signaling pathway, which plays a key role in the process of TGF-β signal transduction from cell surface to nucleus. In the lung tissue of bronchial asthma, TGF-β1 can activate the Smad2 / 3 pathway by direct autocrine and paracrine pathways, up-regulate the expression of vascular endothelial growth factor and platelet-derived factor, activate fibroblasts and induce myofibroblast transformation and ECM synthesis and deposition, and promote airway remodeling.Smad3 can also activate the activity of α-SMA promoter and the expression of α-SMA protein induced by TGF-β1, thereby regulating the differentiation of myofibroblasts.Smad7 can inhibit TGF-β activity and reduce airway remodeling by competing with Smad2/3 for TGF-β receptors [10]. Matrix metalloproteinases are a family of proteases with similar structure, which are responsible for the remodeling of ECM (extracellular matrix), and can selectively degrade ECM components, the most important of which is MMP-9. The exposure of neutrophils to allergens produces MMP-9, and Th2 cytokines IL-4 and IL-1 increase TGF-β1 expression to stimulate MMP-9 production. The synthesis and catabolism of ECM are in dynamic balance [11]. TGF-β1 can activate the expression of matrix metalloproteinase gene. At the same time, MMP-9 can release a large number of cytokines including TGF-β1 by degrading ECM, and further promote cell proliferation and differentiation.MMP-9 can also degrade the collagen components of blood vessels, accelerate the migration of smooth muscle cells to the vascular matrix, expand the surface area of blood vessels, make the blood vessel wall thinner and promote the formation of new blood vessels.MMP-9 can also make vascular endothelial growth factor (VEGF) release angiostatin to participate in the formation of new blood vessels. The expression of vascular endothelial growth factor (VEGF) protein in serum and sputum of patients with moderate to severe asthma was significantly increased and positively correlated with the severity of the disease. VEGF is a glycosylated secretory polypeptide factor, which is secreted by alveolar bronchial epithelial cells, smooth muscle cells and fibroblasts. VEGF can increase the permeability of vascular wall and promote the formation of vascular network. VEGF promotes the occurrence and development of airway inflammation in asthma, enhances the permeability of blood vessels, causes tissue edema, causes dyspnea, and further aggravates the process of airway remodeling [5]. So, TGF-β1 and MMP-9 play a synergistic role in promoting airway remodeling [12].

2.2 The Understanding and Research Progress of BA in Traditional Chinese Medicine

In ancient medical books of traditional Chinese medicine, "asthma" is mostly diagnosed and treated as "asthma" disease, alias "Gasou, Shangqi, Chuanjia" and so on. It is characterized by wheezing in the throat, difficulty in breathing and shortness of breath, and even wheezing can not lie down. There is no name of asthma in *NeiJing*, but there are records of symptoms, etiology and pathogenesis. As *SuWenYinYangDaLun* said, "yin competes in the inside, yang disturbs the outside, sweat is not hidden, four reverses rise, from the smoked lung, make people wheezing". *JinGuiYaolue* is called "Shangqi", and it is believed that phlegm is the key to the disease. *BingYinMaizheng*: the cause of asthma, phlegm retention and stagnation, lurking in the interior. In the Qing Dynasty, the pathogenesis was summarized as "internal congestion of qi, external sense of non-time, and diaphragmatic phlegm of glue-solidification" by *ZhengZhiHuiBu*. The occurrence of asthma is caused by the hidden phlegm in the lung, exogenous, diet, emotion, fatigue and other causes. As a result, Phlegm obstructing airway, pulmonary failure of descension, rebellion of lung-qi, Phlegm gas fight. Different syndromes of asthma treatment herbs is also different. *JingYueQuanShu*: "Asthma has a long root, in case of cold hair, or those who are ready to work, also known as asthma. *ZhangShiYiTong* said: "asthma syndrome is mostly cold package heat evil, in case of cold hair, wheezing dyspnea, phlegm in the lung collaterals, must use vomiting method to lift the scattered, not pure cold, often with pungent, Small qinglong decoction is the best to stinulate vomiting, years of high gas weak people avoid vomiting". *JinGuiYaolue* recorded: patients with phlegm retention should be treated with mild treatment.

3. Research Progress of Small Qinglong Decoction in the Treatment of BA

Small qinglong decoction is contained in *Treatise On Old Damage Diseases* and is one of the representative prescriptions for asthma, it is composed of herba ephedra, cinnamomum cassia, herbaceous peony, manchurian wildginger, dried ginger, baked licorice, pinellia tuberifera, Schisandra chinensis eight herbs. It has the effect of jiebiao and dispelling cold, warming lung to reduce watery phlegm. It is a classic prescription for the treatment of "external cold and internal drink". herba ephedra and cinnamomum cassia in the

prescription should reverse restriction principal drug, induces sweating and dissipating cold to diaphoresis relieving superficies, herba ephedra can dispersing lung qi to relieve cough and asthma, cinnamomum cassia can transforming qi and moving water to warm up the drink. manchurian wildginger and dried ginger are adjuvant drug, warming lung to reduce watery phlegm, aiso can help herba ephedra, cinnamomum cassia diaphoresis relieving superficies. However, there is phlegm itself, spleen-lung deficiency, if it is purely use pungent and warming drugs to open the aperture, fear of consuming and injuring lung qi, it is accompanied by schisandra chinensis to lung-arresting and cough-relieving therapy, herbaceous peony to nourish nutrient blood. pinellia tuberifera as adjuvant medicine to drying wet phlegm and stomach drop inverse. Baked licorice as minister drug, it can not only tonifying qi regulating stomach, but also reconcile Xinshen Acid. Clinically, it is mostly used to treat respiratory diseases such as chronic bronchitis, bronchial asthma, chronic obstructive emphysema, pulmonary heart disease, and pulmonary interstitial fibrosis [7]. At present, although the basic experiments on the treatment of BA with smallqinglong decoction are visible, few studies have reported the positive effects of smallqinglong decoction alone in the treatment of BA airway remodeling, and the mechanism is not clear.

Smallqinglong decoction is widely used in the clinical treatment of BA [1, 7, 13]. Modern pharmacological studies have found that the drug composition of smallqinglong decoction, the effective components of ephedra are ephedrine, flavonoids, volatile oils, etc, can sweating, relieving cough and asthma, analgesic and anti-inflammatory, anti-allergy [14]. The effective components of Ramulus cinnamomi were volatile oil, organic acid, glycosides and so on, can thermal regulation, analgesia,

antibacteria, anti-inflammatory, anti-allergic [15]. Dried ginger contains volatile oil, gingerols and other active ingredients, it has anti-inflammatory, antioxidant, antipyretic and other effects [16]. Asari Radix et Rhizoma contains volatile oil, lignans, fatty acids and other active ingredients. It has antiviral, antibacterial, antitussive and antiasthmatic, anti-inflammatory and analgesic effects [17]. Schisandrae Chinensis Fructus contains lignans, polysaccharides, volatile oil and other effective components, which have the effects of immune regulation, antipyretic analgesia, sedation and cough relief [18]. Peony contains monoterpenes and glycosides, triterpenes and steroids, flavonoids and other effective components, which have the effects of immune regulation, anti-inflammatory and liver protection, anti-hypertension and analgesia [19]. Pinellia ternata contains alkaloids, organic acids, phenolic acids and other active ingredients, which has anti-inflammatory, antibacterial, antitussive and expectorant effects [20]. The main active ingredients of licorice are triterpenoid saponins and flavonoids, which have anti-inflammatory, anti-viral, immune regulation and other effects [21]. Gao Xue [22] and them used snallqinglong Decoction in the treatment of patients with bronchial asthma. Studies have shown that Xiaoqinglong decoction can improve mucosal edema and lumen obstruction by inhibiting the release of inflammatory mediators, which can significantly reduce airway hyperresponsiveness and has a certain effect on blocking airway remodeling. Gao Yichao [23] and them used smallqinglong decoction to treat bronchial asthma with external cold and internal fluid retention syndrome, which proved to be effective. It can reduce the body 's inflammatory response, improve the patient 's respiratory function, and relieve the clinical symptoms such as asthma. Meng Yong [24] experiment has verified that Xiaoqinglong Decoction can effectively inhibit mucus secretion and airway inflammation in asthmatic rats, and alleviate the symptoms of asthmatic rats. The mechanism may be related to the inhibition of mucin Muc5 ac and Muc5 b levels and the reduction of mucus hypersecretion. Liu Gaixia [25] believes that smallqinglong decoction can effectively improve inflammatory response and inhibit airway remodeling in children with acute asthma attack, which is superior to western medicine alone. Yang Liying 's experiments [26] show that Xiaoqinglong Decoction can reduce the concentration of MMP-9 and TIMP-1 in serum and improve airway remodeling in asthma. And, different age, the effect is also different: the younger the animal, the more obvious the improvement effect. Jieyu's experiments [27] show that smallqinglong Decoction could improve airway remodeling in asthmatic mice by reducing airway inflammation and inhibiting the expression of IL-13 and TGF-β1 in lung tissue. Siaoqinglong decoction can reduce airway inflammation and airway hyperresponsiveness in patients with asthma, and can intervene in airway irreversible airway remodeling.

Wind-cold is the main cause of asthma attack, pathological factors are blamed on phlegm, phlegm in the lung becomes pathogenic nosogenic root. therefore “external infection outside, Phlegm congestion inside”, “phlegm gas knot, failure of the lung to descend” develop into asthma. About the name of smallqinglong decoction. Chinese Medicine A Comprehensive Dictiongnary Of Ancient And Modern Chinese once explained the name of a qinglong, “taking its meaning of turning over the waves to return to the sea, not to rise to the sky for the rain”. Zhongjing pointed out that “typhoid exopathogenic factors are indissoluble, there is aqueous vapour under the heart, retching fever and cough, or thirsty, or Li, or choke, or difficulty in micturition, lower abdominal fullness, or asthma, smallqinglong decoction hosting”. Smallqinglong decoction has the effect of relieving cough and asthma, warming lung to reduce watery phlegm, is treating bronchial asthmaeternal's eternal famous prescription. It is basically consistent with the pathogenesis of asthma, reflecting the principle that “patients with phlegm and fluid retention should be treated with warm medicine”. Smallqinglong decoction is widely used in clinical practice, indicating that Xiaoqinglong Decoction is a reliable prescription for the treatment of bronchial asthma [1, 28, 29].

4. Conclusion

In summary, this paper briefly describes a mechanism of action of Xiaoqinglong decoction on airway remodeling in asthma, and provides a new idea for the treatment of airway remodeling with traditional Chinese medicine monomer and compound in the future. In asthma airway remodeling, TGF-β1 / Smad pathway has been widely studied by scholars at home and abroad in recent years, which has been proved to have abnormal activation level in the pathogenesis of asthma. By intervening the above pathways, the process of airway remodeling in asthma can be effectively inhibited, suggesting potential value targets and scientific research directions for

the prevention and treatment of airway remodeling in asthma.

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