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Cilia Function as a Target for Respiratory Diseases and TCM

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Abstract

Cilia in the lungs have a primary role in many respiratory diseases. Disruption of ciliated epithelial cell functions results in excess mucus in the airways, termed watery phlegm according to the Traditional Chinese Medicine Theory. Traditional Chinese Medicine prescription to treat respiratory diseases caused by watery phlegm attenuate cilia shortening, aid the clearance of ciliated epithelial cells and reduce excess mucus in the airways. Further studies are required to determine the role and mechanism of Traditional Chinese Medicine decoction and its analogous formulae and this might help develop new drugs for the treatment of respiratory diseases.

Keywords: Cilia function; Mucus; Watery phlegm; Traditional Chinese medicine

Introduction

Cilia was discovered around 1674-1675 and the research was largely focused on motile cilia's structure, movement and biogenesis at first, but with the discovery of intraflagellar transport and the link between primary cilia ciliogenesis and disease, research on primary cilia has dramatically increased [1]. Cilia not only plays the critical role in lung disease [2], but also has ciliopathy component in any other diseases within the field of cancer and neuroscience [3,4]. The function of cilia is connected with other mechanical and chemical signaling including the autophagy [5], which suggests that studies of cilia in respiratory diseases and other diseases will be more important in future and that regulating the function of cilia may lead to new therapeutics. In this review, we focus on the cilia function as a target for respiratory diseases and the effect of Traditional Chinese Medicine (TCM) on cilia function.

Cilia function and impaired mucociliary clearance

Cilia in the lungs have a primary role in innate defense mechanisms and the clearance of mucus. Under normal circumstances, the mucociliary escalator covers most of the bronchus, bronchiole and nasal cavity, which is composed of ciliated epithelium and goblet cell that secrete mucus. Ciliated epithelial cells eliminate particles and pathogens trapped in mucus from the airways. In pulmonary disease, disruption of airway epithelial cell functions results in impaired mucociliary clearance. This is followed by reepithelialization dominated by goblet cells resulting in excess mucus production, which might promote susceptibility to respiratory infections [2]. Chronic inflammatory disease of the airways, such as chronic obstructive pulmonary disease (COPD) and asthma, are characterized by the differentiation of goblet cells, mucus hypersecretion and cilia dysfunction [6,7]. Furthermore, airway ciliary dysfunction is associated with adverse postoperative outcomes in some congenital heart disease patients [8]. Targeting cilia function would improve mucociliary clearance and reduce excess mucus, which may benefit treatment of respiratory diseases.

The mechanisms of ciliated epithelial cell dysfunction

The mechanisms of ciliated epithelial cell dysfunction remain unclear, but are thought to involve a reduction in epithelial cell cilia length and airway epithelial cell death leading to cilia shortening and altered airway function. Autophagy has multifunctional roles in the regulation of organelle homeostasis and protein turnover, which further influences the progression of human diseases and lung disease [9]. In the process of cilia dysfunction, selective autophagy for cilia components is important. Cloonan et al. coined the term ciliophagy to describe the selective autophagy that regulates cilia dysfunction in COPD and which degrades ciliary proteins by the autophagy-dependent pathway and correlates with cilia shortening [10]. Under pathological circumstances, oxidative stress and other factors cause ciliary protein damage, which promotes the formation of autophagosomes dependent on the autophagy proteins Light Chain 3B (LC3B) and beclin 1.

Qi et al. [11] found that ovalbumin (OVA) exposure caused the reduction in cilia length compared with that observed in the normal group and viable airway cells displayed an increase in the number of autophagosomes containing large amount of degradative autophagic vacuoles and few mitochondria. The above verified that asthma also has cilia dysfunction-ciliophagy [11]. We further confirmed that TCM, which increased mucus clearance, influenced the function of ciliated epithelial cells and had a satisfactory therapeutic effect [11]. The role of ciliophagy in other lung diseases should be investigated to better understand the mechanisms involved in ciliated epithelial cell dysfunction.

Anti-respiratory disease TCM for watery phlegm modulates mucus

TCM prescription treats cold fluid, cough, asthma and influenza viruses [12] caused by watery phlegm. Many decoction analogous formulae mentioned by Zhang Zhongjing in the TCM textbook *Shang Han Lun* (*Treatise on Cold Damage Diseases*) is used to treat these respiratory diseases [13] and the proportion of analogous formulae is greater than 80.2% [14]. Xiaoqinglong decoction analogous formulae such as the Xiaoqinglong (XQL), Mahuang Xingren Shigao Gancao, Mahuang Fuzi, Houpu Mahuang and Daqinglong decoctions, have been widely used for bronchitis, asthma, cnidosis, pneumocardial disease [14].

Most studies of XQL focused on relieving cough and fever, inhibiting inflammation and anaphylaxis and reducing airway hyper-reactivity and remodeling [15,16]. We further examined the change and mechanisms of XQL on mucus hypersecretion in the airways using an OVA-induced asthma mouse model and found that XQL reduced the amount of airway mucus, which helped to improve asthma [11].

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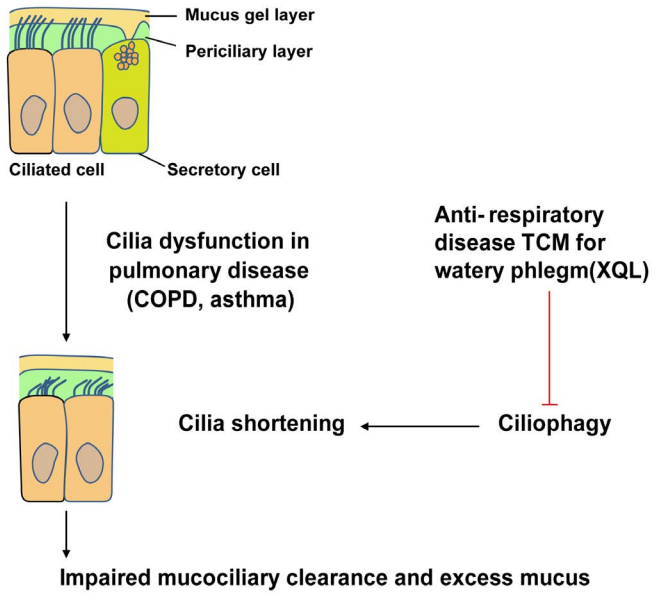

Figure 1: Cilia function as a target for respiratory diseases and the effect of Traditional Chinese Medicine (TCM) on cilia function

However, further study is required to determine the role and mechanism of XQL decoction analogous formulae.

Anti-Respiratory Disease TCM for Watery Phlegm Modulates Cilia Function

Ciliophagy reduces mucociliary clearance and the subsequent elimination of particles and pathogens from the airways and promotes susceptibility to airway diseases [10]. Anti-respiratory disease TCM as a modulator of mucus should be further examined to determine its effect on cilia function including the length of cilia and ciliophagy, which are related to airway mucus clearance.

As a famous TCM prescription to treat asthma and influenza viruses [12,13], XQL contains eight herbal components including *Ephedrae* (*Ephedra sinica* Stapf, *Ephedra intermedia* Schrenk & C.A. Mey.), Ramulus *Cinnamomi* (*Cinnamomum cassia* (L.) J. Presl), Rhizoma *Zingiberis* (*Zingiber officinale* Roscoe), Radix *Asari* (*Asarum heterotropoides* f. *mandshuricum* (Maxim.) Kitag., *Asarum sieboldii* Miq.), Fructus *Schisandrae* (*Schisandra chinensis* (Turcz.) Baill.), *Glycyrrhiza Uralensis* (*Glycyrrhiza uralensis* Fisch.), Rhizoma *Pinelliae* (*Pinellia ternata* (Thunb.) Makino) and Radix Paeoniae Alba (Paeonia lactiflora Pall.). Based on the dosage by Xie et al. [17], we found that XQL, which was orally administered, restored cilia length, reduced the number of degradative autophagic vacuoles and increased the number of mitochondria in the tracheal epithelium compared with the asthma model group [11]. The expression of LC3 was lower in the tracheal epithelium of the XQL-treated group than in the asthma model group [11].

With the fingerprints of high performance liquid chromatography for XQL's single herb and herbal pair including Mahuang-Gancao, Mahuang-Guizhi, Shaoyao-Guizhi, Shaoyao-Gancao, Wuweizi-Xixin, we discussed main components of a single herb and herbal pair and summarized the character of the Xiaoqinglong decoction [18], but future studies should determine the different roles of these herbal components to modulate cilia function.

Conclusion

Ciliophagy impairs airway mucus clearance. Reducing ciliophagy allows airway function recovery and mucus homeostasis of the airways, suggesting this pathway might be a new target of pharmacotherapy. Treatment with XQL attenuated mucus secretion in the airways, improved cilia length and reduced ciliophagy. Further studies should investigate the different roles and mechanisms of XQL decoctions and analogous formulae to modulate cilia function, which might be a potential target of the treatment to pulmonary diseases (Figure 1).

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Disclosure statement

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