



MINI REVIEW

Environmental pollutants damage airway epithelial cell cilia: Implications for the prevention of obstructive lung diseases

Yu Cao, Miao Chen, Dan Dong, Songbo Xie  & Min Liu 

College of Life Sciences, Shandong Provincial Key Laboratory of Animal Resistance Biology, Collaborative Innovation Center of Cell Biology in Universities of Shandong, Institute of Biomedical Sciences, Shandong Normal University, Jinan, China

Keywords

Airway epithelium; environmental pollutant; lung disease; mucociliary clearance.

Correspondence

Songbo Xie, College of Life Sciences, Shandong Normal University, Jinan, Shandong 250014, China.
Tel: +86-531-8618-2516
Fax: +86-531-8618-2518
Email: xiesongbo@sdsu.edu.cn

Min Liu, College of Life Sciences, Shandong Normal University, Jinan, Shandong 250014, China.
Tel: +86-531-8618-2516
Fax: +86-531-8618-2518
Email: minliu@sdsu.edu.cn

Received: 22 November 2019;
Accepted: 4 January 2020.

doi: 10.1111/1759-7714.13323

Thoracic Cancer **11** (2020) 505–510

Abstract

Mucociliary epithelium lining the upper and lower respiratory tract constitutes the first line of defense of the airway and lungs against inhaled pollutants and pathogens. The concerted beating of multiciliated cells drives mucociliary clearance. Abnormalities in both the structure and function of airway cilia have been implicated in obstructive lung diseases. Emerging evidence reveals a close correlation between lung diseases and environmental stimuli such as sulfur dioxide and tobacco particles. However, the underlying mechanism remains to be described. In this review, we emphasize the importance of airway cilia in mucociliary clearance and discuss how environmental pollutants affect the structure and function of airway cilia, thus shedding light on the function of airway cilia in preventing obstructive lung diseases and revealing the negative effects of environmental pollutants on human health.

Introduction

The human airway is a dichotomous hollow tubular structure mainly lined by ciliated, brush, goblet, and basal cells.¹ These cells form a continuous physical, secretory, and regulatory barrier of epithelium, which functions to protect the airway and lungs from inhaled pathogens and environmental pollutants.² Basal cells are stem/progenitor cells that differentiate into ciliated cells and goblet cells in response to injury and repair.³ Goblet cells secrete the mucus and mucins that comprise the mucus gel layer, an important component of the mucociliary escalator.³ Airway ciliated cells dominate the epithelium and coordinate with the goblet cells to constitute the first line of defense.⁴ The concerted in-plane beating of all ciliated cells propels the mucus layer forward, thus driving mucociliary clearance (MCC).

Abnormalities in both the airway cilia structure and function lead to impaired mucociliary clearance.⁵ Cilia dysfunction has been implicated in a variety of lung diseases, such as cystic fibrosis, immotile cilia syndrome, bronchial asthma, and chronic obstructive pulmonary disease (COPD).^{6–10} For example, Yaghi and Dolovich have discussed the importance of airway epithelial cilia in the initiation or progression of obstructive lung diseases¹¹; Price and Sisson have highlighted the redox modulation in airway ciliary function and diseases.¹² Here, we review the structure and function of airway cilia, and focus on the influence of environmental pollutants on ciliary beating and their outcomes. This review will shed light on the function of airway cilia in preventing obstructive lung diseases and reveal the negative effects of environmental pollutants on human health.

Structure and function of airway cilia

Cilia are highly specialized hair-like structures that protrude from the surface of epithelium. They are mainly composed of microtubule-based axoneme, surrounded by a plasma membrane.^{13–16} Cilia can be typically divided into primary nonmotile cilia and motile cilia, depending on the axoneme structure. The axoneme of primary cilia is arranged in a ring of nine peripheral doublet microtubules (termed a 9 + 0 axoneme), and the axoneme of a motile cilium has two single microtubules at the center of the nine peripheral doublet ring (termed a 9 + 2 axoneme).^{15,17–22} In addition, the peripheral doublets of motile cilia are attached by inner and outer dynein arms, which allow ciliary movement by ATP-dependent conformational alterations. Aberrance in ciliary axoneme and dynein arm-associated structures can result in impaired ciliary movement.

The airway cilia that line the pseudostratified epithelium of respiratory tract are motile with a 9 + 2 axoneme pattern, and each airway epithelial cell has more than 200 cilia on its surface. These cilia beat almost synchronously, thus driving continuously oral-directed transport of mucus, termed mucociliary clearance (MCC). MCC is a complex and orderly cycle program,²³ a critical event for fluid secretion and immune defense. The cilia start to move from the resting position by bending laterally and backward, which is called the recovery swing. When a cilium returns to the resting position, its tip points in the direction of propulsion; this stage ends and the resistance of mucus flow is minimized. The ciliary oscillations are coordinated by a heterogeneous wave pattern that couples the oscillating frequency of each cilium with the oscillating frequency of the adjacent cilia to promote the directional transport of the mucus.²⁴ The wave swing is spread by the antirelaxation coordination but the mechanism of adjusting the synchronous swing of multiple cilia is not clear. In addition, the effectiveness of MCC is affected by a diversity of factors, including cilia numbers and their structure, humidity, temperature, age, pathogens, and environmental stimuli.^{25–29}

Abnormal ciliary function and lung diseases

Given the importance of MCC in clearance of the inhaled particles and pathogens, inadequate MCC and the resulting decline of the host's lung defense functions can lead to the pathogenesis of various pulmonary diseases such as cystic fibrosis, COPD, and chronic bronchitis.^{30,31} There are many factors that can lead to inadequate MCC, which include impaired fluid secretion, abnormal ciliary function, lack of cough, or the damage of epithelial cells lining the

respiratory tract. Of these, abnormal ciliary function accounts for the majority.

Mounting evidence has revealed that airway cilia that are affected by environmental contaminants exhibit acquired structural or functional abnormalities accompanied by abnormalities in mucociliary clearance.³ For example, sulfur dioxide, sulfuric acid, nitrogen dioxide, and ozone all affect mucus cilia and respiratory function.^{32–36} In physiological conditions, inhaled particles and pathogens can be entrapped and then removed through MCC. However, excessive exposure to environmental pollutants can contribute to abnormal cilia structure and function, thus resulting in inadequate MCC and consequently leading to various lung diseases (Fig 1).

Environmental pollutants

Environmental pollutants are foreign products that change the normal composition and properties of the environment and are directly or indirectly harmful to humans and other organisms.³⁷ They mainly consist of irritating gases and harmful particles, including sulfur dioxide, nitrogen dioxide, ozone, indoor air pollutants, and tobacco particles.³⁸ Environmental pollutants can be divided into three classes: atmospheric pollutants, water pollutants, and industrial pollutants. These can be further divided according to the form of pollutant: gaseous pollutants, liquid pollutants, and solid pollutants; and according to the nature of the pollutant: chemical contaminants, physical pollutants, and biological contaminants.³⁹ The harm of environmental pollutants to the human body is mainly reflected in respiratory mucosa damage and obstructive pulmonary disease because the respiratory tract is the first thing affected by environmental exposure.⁴⁰ Several studies have shown that in environments with air pollution, the cilia in the human respiratory tract become shorter or are missing, which affects their ability to clear the respiratory tract. For example, when experimental animals were exposed to higher concentrations of ozone (4 ppm), it was observed that the vesicles of the ciliated membrane and the structure of the tracheal cilia were damaged.⁴¹ In addition, mucosal cilia clearance may be inhibited due to factors such as quantity of contaminant concentration and duration of exposure.

Sulfur dioxide

Sulfur dioxide is one of the major air pollutants in industrialized countries. The main outdoor source of sulfur dioxide is the combustion of sulfur-containing minerals, mainly coal and petroleum, in the commercial industry.⁴² Sulfur dioxide is water soluble and easily inhaled into the respiratory tract where it forms sulfurous acid and sulfuric acid.⁴³ These acids are strong irritants and have burning

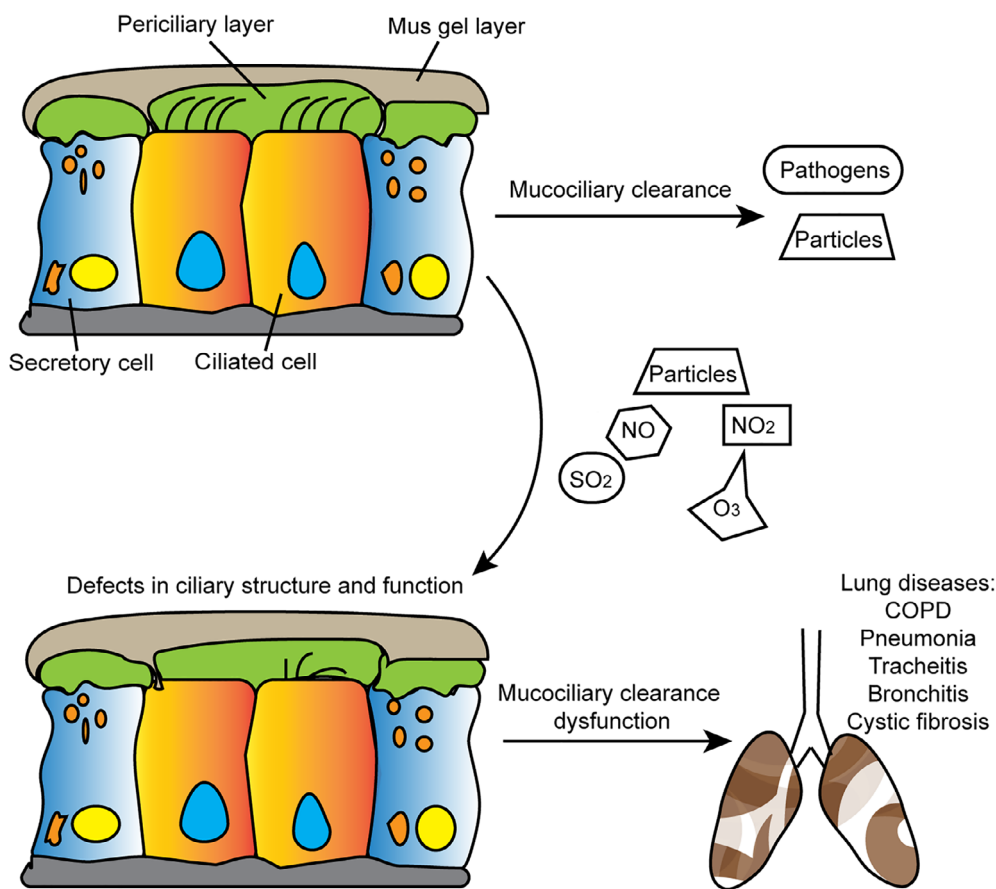


Figure 1 Secretory cells and ciliated epithelial cells constitute the first line of lung defense. Secretory cells produce gel-forming mucins to entrap inhaled particles and ciliated epithelial cells transport them out of the lung through cilia beating. Conversely, some environmental pollutants, including particles, NO, NO₂, SO₂, and O₃, can lead to impaired structure and function of airway cilia, thus resulting in inadequate MCC and consequently leading to various lung diseases.

effects on the human respiratory tract. This leads to lung diseases such as bronchitis and asthma, accompanied by lung pain, cough, phlegm, and other adverse reactions.⁴⁴ Van *et al.* reported that the ultrastructure of the airway epidermis of guinea pigs changed after 30 minutes of sulfur dioxide treatment.⁴⁵ Abraham *et al.* noted that in healthy non-smokers, MCC significantly accelerated after 2.5 hours of exposure to sulfur dioxide, which was caused by an increase in ciliary beat frequency. However, excessive sulfur dioxide caused a decrease in MCC.⁴⁶ Like phytohormones, the effect of sulfur dioxide on cilia is dependent on the concentration; low concentration causes promotion and high concentration causes inhibition.

Nitrogen dioxide

Nitrogen dioxide is one of the most common air pollutants. It is mainly produced by various combustion processes, especially in industrial and urban areas.⁴⁷ Nitrogen dioxide

is very harmful to the human body. Human lung function is damaged with even a little exposure to nitrogen dioxide. If exposed to nitrogen dioxide for a long time, the chance of respiratory infections increases, as well as the risk of permanent organic lesions in the lungs.⁴⁸ Helleday *et al.* studied a significant decrease in ciliary beat frequency in healthy people exposed to nitrogen dioxide and found that it may be important for MCC function.⁴⁹ Blomberg *et al.* found that nitrogen dioxide had no significant effect on the MCC of the upper respiratory tract, from the tip of the nose to the midpoint of the trachea, but that it did reduce the MCC of the lower respiratory tract, including the lower half of the trachea and the lungs.⁵⁰ Like sulfur dioxide, nitrogen dioxide affects the respiratory tract by affecting MCC.

Indoor air pollutants

Formaldehyde, acrolein, phenols, and ammonia, which are usually present in indoor air pollutants, have an effect on

ciliary oscillations and structure, as well as mucous flow, which may be a cause of respiratory disease.^{51–53} Formaldehyde has the strongest effect, followed by acrolein.^{54,55} After exposure to acrolein, the tip of the cilia is swollen, making the cilia function abnormally; formaldehyde and ammonia reduce the flow of the sputum, which causes functional damage to the MCC.⁵⁶

Smoking

Smoking is a main cause of human disease. Tobacco particles, nicotine, and other chemicals in cigarettes cause serious damage to peoples' heart and lung function and lead to coronary heart disease, COPD, cerebrovascular disease, and cancer.⁵⁷ Smoking also reduces the number of cilia in the respiratory tract, affects the frequency of ciliary oscillations, and thus affects the airway epithelial MCC.⁵⁸ For example, compared with healthy non-smokers, smokers are deficient in cilia with abnormal structures and functions of ciliated cells. Long-term smoking can lead to an increase in the number of abnormal cilia in the bronchi and may damage the tracheobronchial function.⁵⁹ Examination of the nasal mucosa of children exposed to smoke showed a loss of cilia. Electron microscopic analysis of the ultrastructure of cilia showed that smokers had more ciliary abnormalities than non-smokers, including composite cilia and giant cilia, as well as other abnormalities in the microtubules, axon 9 + 2 tissue, and the cilia localizations.⁶⁰ Smoking is also one of the main causes of COPD.

Concluding remarks

Environmental pollutants have been implicated in several lung diseases, such as obstructive pulmonary diseases and bronchitis. Airway cilia are essential for MCC and protect the lungs from diseases caused by environmental pollutants. Emerging evidence reveals that environmental pollutants impair the physiological roles of airway cilia. However, the molecular mechanisms of how environmental pollutants affect the structure and function of airway cilia remain largely unknown. Recent studies reveal that some redox regulatory proteins, including protein phosphatase 2A, protein kinase A, protein kinase C, soluble guanylyl cyclase, and dynein ATPases, are enriched in cilia and play critical roles in regulating airway cilia.¹² It is postulated that oxidants in environmental contaminants lead to redox imbalance and impair airway cilia. More research regarding redox signaling in cilia regulation will likely uncover the molecular mechanism underlying lung diseases induced by environmental pollutants.

In addition, with a more in-depth understanding of airway ciliogenesis and the development of genome editing, it is feasible to cure lung diseases caused by cilia deficiency.

In addition, future studies will explore the details of environmental pollutants, including the type of pollutants, maximum exposure dose, and time that can lead to airway cilia defects and dysfunctions of MCC. These studies may help to increase awareness of the damage environmental pollutants cause to airway cilia and provide a basis for establishing environmental protection laws.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (31701216), and Natural Science Foundation of Shandong Province (ZR2017MC008).

Disclosure

The authors declare no conflict of interest regarding the publication of this article.

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