Chapter 6

Chronic *Pseudomonas aeruginosa* Infection as the Pathogenesis of Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD), resulted from tobacco smoking, has an extremely poor prognosis and is a major cause of chronic morbidity and mortality worldwide. In this chapter, we review the role of bacterial infection on the pathogenesis of COPD, with a particular focus on *Pseudomonas aeruginosa*. Chronic infection with *P. aeruginosa* has been shown to contribute to COPD pathogenesis under certain conditions. In addition, *P. aeruginosa* is a major factor influencing severe symptoms, acute exacerbation, and the progression of COPD. Treatment for chronic *P. aeruginosa* infection may become a new strategy for addressing COPD.

Keywords: chronic inflammation, emphysema, acute exacerbation, bronchiectasis, microorganism, pathogenesis

1. Introduction

Chronic obstructive pulmonary disease (COPD) is induced by mainly tobacco smoking. The patients of COPD complained of cough, sputa, or exertional dyspnea. Compared to the patients with bronchial asthma, COPD has an extremely poor prognosis. Approximately 3,200,000 COPD patients died worldwide in 2015 [1]. The mortality is estimated to be ≥8-fold that of bronchial asthma. In this chapter, we review the role of bacterial infection on the pathogenesis of COPD, with a particular focus on *Pseudomonas aeruginosa*.

2. Chronic obstructive lung disease (COPD)

COPD is a relatively common disease characterized by respiratory symptoms and airflow limitation, usually caused by smoking. A mixture of small airway disease and parenchymal destruction caused airflow limitation. COPD patients complained of cough, dyspnea, and sputum production. Acute exacerbation frequently occurs after an acute respiratory infection. The acute exacerbation leads to more severe airflow limitation [2]. Sometimes, COPD patients are accompanied with bronchiectasis. These patients caused more frequent acute exacerbations and severe airway obstruction. Also, these patients demonstrated pathogenic microorganisms and mortality [3]. At present, there is no universally effective treatment for COPD. Some treatments just relieve the symptoms, while others could slow the progression of the disease. The most effective treatment is stopping smoking. Bronchodilators are the mainstay of available treatment options for COPD. There are several types of bronchodilators. Long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), or a combination of these agents is used for COPD patients, since long-acting medication is preferred. For the patients complicated with bronchial asthma, known as asthma-COPD overlap (ACO), inhaled glucocorticoids (ICSs) can be used. Also, ICSs can be used for patients with frequent COPD exacerbation. Short-acting beta agonists (SABAs) and short-acting muscarinic anticholinergics (SAMAs) are used to relieve symptoms, such as exertional dyspnea. Since theophylline can be given orally, it can be used for patients who cannot inhale medications. Advanced COPD patients with hypoxemia are administered with long-term oxygen therapy (LTOT). Rehabilitation programs are also important. They can be effective; however, they do not improve the outcome. Lung volume reduction surgery is performed in select patients with COPD; however, the candidate patients are limited. Also, lung transplantation is rarely done because of lack of donors [4]. Antioxidants, mucolytics, antiproteases, and antifibrotics are sometimes used; however, these drugs are not a mainstay for COPD. Anti-inflammatory drugs such as phosphodiesterase 4 inhibitors are used to reduce airway inflammation. Also, kinase inhibitors, chemokine receptor antagonists, innate immune mechanism inhibitors, and statins are developing [5]. However, these new treatments are still insufficient to demonstrate the evidence for caring COPD. As such, a novel therapy for COPD is required.

3. *Pseudomonas aeruginosa*

P. aeruginosa is a glucose non-fermenting Gram-negative bacillus. The size of *P. aeruginosa* is 0.7 × 2 μm. *P. aeruginosa* is localized in the natural environment such as in soil and freshwater. *P. aeruginosa* does not show usually pathogenicity in healthy individuals but, however, causes infection mainly in immunocompromised patients [6]. *P. aeruginosa* is well known to cause chronic infection in bronchiectasis as well as COPD. Biofilm formation is important for chronic infection. A biofilm is a self-produced polymer matrix consisting of polysaccharides, protein, and DNA. Bacteria are embedded in biofilm. The polysaccharide alginate is the major components of the *P. aeruginosa* biofilm matrix. *P. aeruginosa* escapes from host immunity and antibacterial drugs using biofilms [7, 8].

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4. *P. aeruginosa* and lung diseases other than chronic obstructive pulmonary disease

P. aeruginosa is often detected in ventilator-associated pneumonia and nosocomial pneumonia. Moreover, bronchiectasis is easily colonized by *P. aeruginosa* [9]. *P. aeruginosa* infection is a risk factor for mortality and morbidity in cystic fibrosis patients [10]. *P. aeruginosa* sometimes produces mucinous materials, so-called mucoid *P. aeruginosa*. Gibson et al. reported that mucoid *P. aeruginosa* contributes to the progression of cystic fibrosis compared to non-mucoid *P. aeruginosa* [11]. *P. aeruginosa* infection in non-cystic fibrosis bronchiectasis patients induces more severe impairment of the pulmonary function, although the rate of decline in the pulmonary function is not affected [12].

5. *P. aeruginosa* and chronic obstructive pulmonary disease

5.1. Steady status of COPD and *P. aeruginosa*

Numerous studies have characterized the lung microbiome of healthy adult subjects using BAL samples. The most common phyla consistently observed have been *Bacteroides*, *Firmicutes*, and *Proteobacteria* in the phylum level. Prominent genera among healthy controls are *Prevotella*, *Veillonella*, *Streptococcus*, and *Pseudomonas*. Tobacco smoking alters the microbial constitution of the upper airways [13]. Erb-Downward et al. reported that *Pseudomonas*, *Streptococcus*, *Prevotella*, *Fusobacterium*, *Haemophilus*, *Veillonella*, and *Porphyromonas* were observed in COPD lungs [14]. *P. aeruginosa* is often observed in the sputum of patients with COPD. Rosel et al. reported that *P. aeruginosa* was colonized in one-quarter of patients with COPD during steady status [15]. *P. aeruginosa* was detected in 4–34.7% of sputum samples from COPD patients [16–20]. *P. aeruginosa* causes chronic infections in COPD [21], and especially COPD patients accompanied with bronchiectasis are easily colonized with *P. aeruginosa*. COPD patients with *P. aeruginosa* colonization have a worse disease activity than COPD patients without *P. aeruginosa* colonization. Desai et al. conducted a longitudinal prospective observational study of COPD. They found that the average of breathlessness, cough, and sputum scale (BCSS) score was higher during the periods of colonization compared to periods without colonization. Colonization was associated with a clinically significant worsening of daily symptoms, even in the absence of clinical exacerbation [22]. These findings suggest that novel therapies that decrease the bacterial colonization may be able to improve the daily symptoms and quality of life in COPD patients.

5.2. Acute exacerbation of COPD and *P. aeruginosa*

Acute exacerbation of COPD is defined as a worsening of the respiratory condition, such as coughing, sputum production, and dyspnea, beyond daily physiological fluctuations and requiring additional treatment. COPD patients with acute exacerbation document a worse quality of life as well as decrease of pulmonary function. Finally, COPD patients with acute

exacerbation result in lower mortality [9]. Acute exacerbation mainly occurs due to airway infections. The relationship between COPD and *P. aeruginosa* infection in acute exacerbation of COPD has already been reported [23–26]. However, bacteria other than *P. aeruginosa* can also cause acute exacerbation of COPD. Indeed, infection with a new strain of *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae* is strongly associated with the occurrence of exacerbation. *H. influenza* (20–30%), *S. pneumoniae* (10–15%), and *M. catarrhalis* (10–15%) were causative bacteria for acute exacerbation. *P. aeruginosa* accounted for only 5–10% of causative bacteria. Infection of respiratory viruses has also been shown to cause exacerbations. However, it is difficult to identify the specific respiratory viruses because of technical problems. *P. aeruginosa* is less frequently detected from the sputum in COPD patients with acute exacerbation than in those without exacerbation. However, acute exacerbation caused by *P. aeruginosa* generally produces a more severe clinical condition than that caused by other pathogens [26].

5.3. Progression of COPD and *P. aeruginosa*

The relationship between disease progression and *P. aeruginosa* infection in COPD patients is not fully understood. Bronchiectasis, a percentage of forced expiratory volume in 1 s (%FEV1) of <35%, systemic steroid use, and antibiotic therapy within the preceding 3 months increased the risk of *P. aeruginosa* colonization [13, 23, 24]. The detection rates of *H. influenza* and *P. aeruginosa* were reported not to be associated with the severity of emphysematous changes [26, 27]. However, chronic *P. aeruginosa* infection was recently reported to be associated with severe obstruction in COPD patients [28]. Hospitalized COPD patients with acute exacerbation by *P. aeruginosa* demonstrated worse lung function, greater dyspnea, and more hospitalizations over the previous year. Therefore, *P. aeruginosa* infection is commonly observed in COPD patients and has been found to cause severe symptoms of COPD, the development of severe acute exacerbation, disease progression, and a poor prognosis.

6. Pathogenesis of chronic obstructive pulmonary disease

The pathogenesis of COPD is considered to be chronic airflow limitation results from an abnormal inflammatory response to the inhaled particles and gasses in the lung in susceptible smokers. There is a famous hypothesis that a protease-antiprotease imbalance leads to the progression of the destruction of alveoli [2]. Alveolar cell loss through apoptosis might contribute to the pathogenesis [29–31]. There are many animal models for COPD, including elastase, cigarette, inhaled gasses, and gene-targeted models. As COPD models, administration of papain or porcine pancreatic elastase model is well known [32]. Neutrophil elastase and proteinase-3, but not non-elastolytic enzymes, such as bacterial collagenase, caused COPD-like changes [33–35]. Cigarette smoking is a major factor inducing the development of COPD. Long-term cigarette smoking caused macrophage-predominant inflammation and airspace enlargement in animal models similar to those found in humans [36]. Potential mechanisms include high concentrations of reactive oxygen species (ROS) [37], oxidative stress

[38], and matrix metalloproteinase (MMP)-12 [39, 40]. Inhaled stimuli, such as sulfur dioxide [41, 42], nitrogen dioxide [43], and oxidant [44], have been shown to induce COPD-like lesions in animal models. Ultrafine particles, such as silica, coal dust, diesel exhaust particles, and cadmium, induced focal emphysema [45, 46], chronic airway inflammation [47], and interstitial fibrosis with enlargement of the airspaces [48]. Alveolar wall apoptosis without the accumulation of inflammatory cells, resulting in emphysematous changes, was attained by active caspase-3 [31, 49]. Prednisolone also causes emphysematous changes through apoptosis [50]. Apoptosis in the alveoli resulted in airspace enlargement was also attained by a block of vascular endothelial cell growth factor (VEGF) receptor-2 [51]. Ceramide production, as the second messenger lipid, was induced by apoptosis. Ceramide played a role in induction of inflammation by the blockade of apoptosis by a VEGF receptor antibody. Since ceramide administration provoked the expression of MMP-12, it was considered to be a link between excessive apoptosis and inflammation [52]. Several gene-targeted models demonstrated COPD-like changed; however, the changes were developmental abnormalities rather than the destruction of mature lung tissue. Tight-skin mice [53, 54], pallid mice [55], and beige mice [56] were reported to be models. COPD mimic models by genetically altered techniques have been reported such as the overexpression of collagenase in the lung of transgenic mice [57], the deficiency of the microfibrillar component fibulin-5 and the deficiency of platelet-derived growth factor A (PDGF-A) [58, 59], epithelial restricted integrin $\alpha v\beta 6$ knockout mice [60], fibroblast growth factor (FGF) receptor (FGFR)-3, and FGFR-4-double knockout mice [61]. Mice lacking the surfactant protein D (SP-D) gene [62] and the tissue inhibitor of metalloproteinase-3 (TIMP-3) gene [63] showed COPD-like lesions. These gene-targeted mice provided useful information for understanding the pathogenesis of COPD. However, none of these mice showed the same pathologic changes as those seen with human COPD.

7. *Pseudomonas aeruginosa* as the pathogenesis for chronic obstructive pulmonary disease

Chronic inflammation also plays a pivotal role in its development. Administration of lipopolysaccharide (LPS) to the lungs induced severe inflammation and resulted in airspace enlargement [64, 65]. COPD-like changes, such as goblet cell metaplasia in the larger airways, thickening of the airway walls, and irreversible alveolar enlargement, were attained by repeated administration of LPS [66, 67]. Tumor necrosis factor (TNF)-alpha is a proinflammatory cytokine induced by stimuli such as LPS. We reported that TNF-alpha overexpression mice in the lungs demonstrated pulmonary emphysema-like changes [68, 69]. MMP activation induced alveolar enlargement [68]. Chronic inflammation by TNF-alpha overexpression is considered to play an important role in the development of COPD. Several reports have found that the overexpression of inflammatory cytokines, such as IL-13 and IFN-gamma, resulted in pathologic changes mimicking human COPD [70–72]. These reports also supported the hypothesis that chronic inflammation in the lungs leads to lung tissue destruction, a hallmark of pulmonary emphysema, and chronic bronchitis.

We therefore investigated the role of chronic inflammation in the pathogenesis of COPD. *P. aeruginosa* induced chronic inflammation as previously described. We hypothesized that chronic inflammation, specifically that induced by *P. aeruginosa*, contributed to the pathogenesis of COPD. To test this hypothesis, pathophysiological changes due to chronic *P. aeruginosa* infection in club cell secretory protein (CCSP)-deficient mice were investigated [73]. The nonciliary bronchial epithelium as well as the uterine and urethral ducts expresses CCSP proteins [74]. The anti-inflammatory response could be speculated as the role of CCSP [75]. Therefore, we consider CCSP-deficient mice to be a model susceptible to chronic infection. CCSP-deficient mice with single administration of *P. aeruginosa* demonstrated similar result to wild-type mice [76]. We used *P. aeruginosa*-colonized catheter methods [73]. This chronic status of *P. aeruginosa* infection continued for more than 5 weeks. As a result, these deficient mice showed more severe inflammation in response to chronic *P. aeruginosa* infection than wild-type (WT) mice, and their bronchi were markedly stenotic (**Figure 1**). The mean linear intercept, destruction index, and lung compliance in the CCSP-deficient mice were significantly higher than those in the wild-type mice (**Figure 2**). Severe inflammation leads to the destruction of the alveolar wall, and bronchial stenosis leads to air trapping (**Figure 3**). Chronic infection of *P. aeruginosa* in CCSP-deficient mice demonstrated COPD-like changes [73]. Recent studies attempting to characterize COPD have shown that CCSP is strongly related to COPD progression [77, 78]. CCSP has been reported to play a role in the modulation of pulmonary inflammation during the infection and recovery phases. Our study revealed the important role of CCSP in the chronic infection phase. Chronic *P. aeruginosa* infection might play a distinctive role in the pathogenesis of COPD. However, several limitations exist. Mice have less airway branching than humans and lack respiratory bronchioles. Major species differences between murine and human lung morphogenesis and discrepancies in both the innate and adaptive immunity between the human and murine immune systems exist [79, 80]. We should consider the limitations carefully.

Recently, macrolide treatment has been reported to protect against acute exacerbation. Among some subjects with COPD, taking azithromycin daily for 1 year, when added to the usual

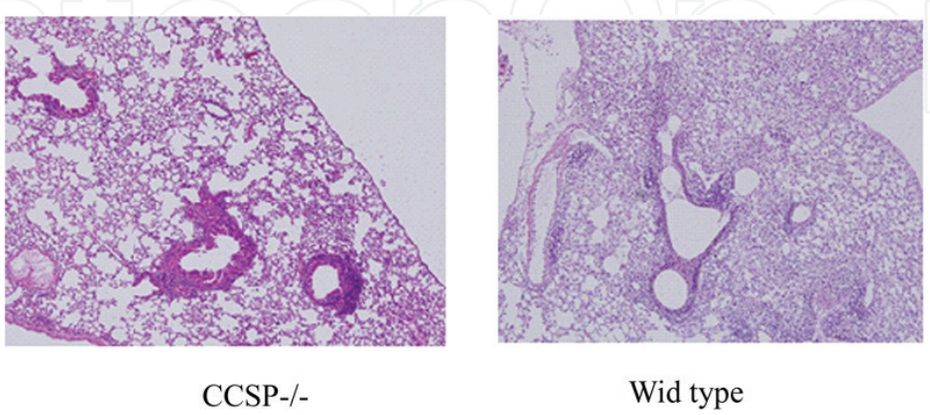

Figure 1. Histology of lungs after chronic *P. aeruginosa* infection. Inflammatory cells infiltrated around the bronchioles and the alveoli septa. The CCSP-deficient model (CCSP−/−) showed bronchial constriction and alveolar enlargement compared to the wild-type model.

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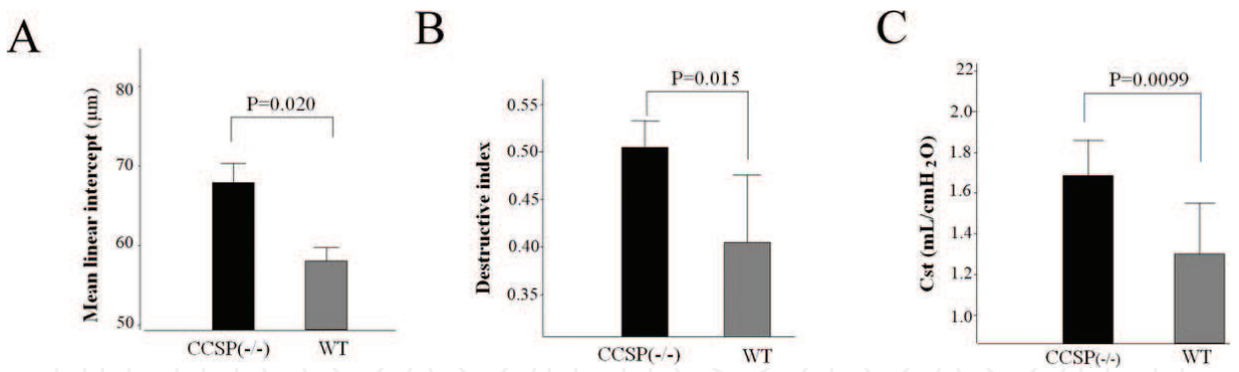

Figure 2. Pulmonary physiology after chronic *P. aeruginosa* infection. (A) Chronic *P. aeruginosa* infection in CCSP-deficient mice (CCSP−/−) resulted in an increase in the mean linear intercept compared to that in wild-type (WT) mice. Furthermore, the CCSP-deficient mice demonstrated a severe destructive index (B). (C) CCSP(−/−) induced elevated pulmonary compliance compared with WT mice. These results indicate that chronic *P. aeruginosa* infection in CCSP-deficient mice induced COPD-like changes.

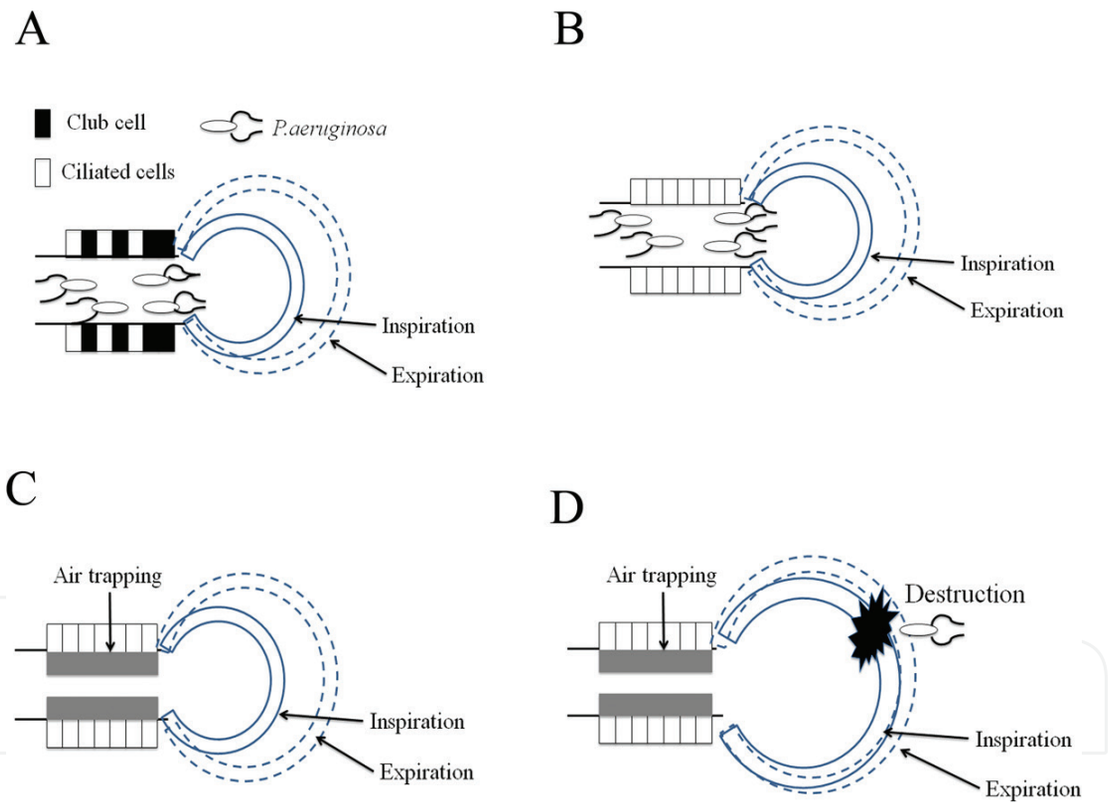

Figure 3. Schematic illustrations of COPD-like changes induced by chronic *P. aeruginosa* infection. (A) When *P. aeruginosa* infected the bronchus, CCSP was secreted from club cells to suppress the inflammation. (B) Since CCSP-deficient mice could not suppress the inflammation through CCSP secretion, serious inflammation occurred. (C) As a result, the bronchus became stenotic, and air trapping occurred. Air trapping progressed, and the alveoli were destroyed. (D) Alveolar destruction due to inflammation also occurred. Finally, the CCSP-deficient mice demonstrated COPD-like changes.

treatment regimen, reduced the frequency of exacerbations and improved the quality of life [81]. Macrolides are known to modulate the inflammation, the so-called immunomodulatory effect, besides antimicrobial effects. In Japan, macrolides are used to treat chronic infection

with *P. aeruginosa*, such as diffuse panbronchiolitis (DPB). These agents might therefore modulate the chronic inflammation induced by *P. aeruginosa*. Further studies are needed to clarify the pathogenesis of COPD. We should seek out direct evidence that chronic *P. aeruginosa* infection is related to the pathogenesis of COPD.

8. Conclusion and future directions

P. aeruginosa infection had never been reported as the pathogenesis of COPD. However, we showed that chronic infection of *P. aeruginosa* contributed to COPD pathogenesis. *P. aeruginosa* is also a major factor influencing the severity of symptoms, acute exacerbation, and progression of COPD. Treating chronic *P. aeruginosa* infection may become a new strategy for treating COPD.

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Conflict of interest

The authors declare that they have no conflicts of interest (COI).

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