1. COPD Pathogenesis from the Viewpoint of Risk Factors

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Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation in the lungs. Smoking is one of the amongst major risk factors for the development of COPD. Environmental pollution, age, and airway hyperreactivity are also the risk factors. The protease-antiprotease imbalance and the oxidant-antioxidant imbalance cause airway inflammation and destruction. The genes related to these balances may contribute to development of COPD pathology. Candidate gene-association studies and linkage analyses have been reported for COPD patients. The alpha-1 antitrypsin, glutathione S-transferase, microsomal epoxide hydrolase, and matrix metalloproteinase, are candidate genes. In acquired factors for COPD pathology, the adenoviral latent infection may enhance airway inflammation, leading to airflow obstruction. The current progress and future visions of genetic predisposition of COPD are discussed.

Key words: Smoking, protease-antiprotease imbalance, oxidant-antioxidant imbalance, Gene-Association Studies, adenoviral latent infection may

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation in the lungs. Although COPD was the 12th largest disease burden in the world in 1990, it is estimated that it will rise to be the fifth largest disease burden by 2020 (1-4). The most important risk factor for the development of COPD is smoking (Fig. 1). However, only 10-20% of chronic heavy smokers develop symptomatic COPD, which indicates that a difference in susceptibility to tobacco smoke injury must exist and may be related to genetic factors (Fig. 2). Candidate gene-association studies and linkage analyses have been reported for COPD patients. We summarized the evidence for the role of the candidate genes in the pathological processes associated with COPD. This review describes the genetic predisposition of COPD. The current progress and future visions of genetic predisposition of COPD are further addressed.

1) Background and Risk Factors of Development of COOD

Chronic tobacco smoking is the major risk factor for the development of COPD, but only a relatively small proportion of smokers actually develop airway obstruction. Although there is a dose-response relationship between FEV1 and the extent of cigarette smoking, smoking history accounts for only approximately 15% of the variation in lung function. That is why the genetic predisposition of COPD may exist in smokers. Although cigarette smoking is the most important risk factor for the development of COPD, allergic airway inflammation, long-standing asthma, air pollutants, and diesel exhaust particles may also cause irreversible airflow limitation such as COPD. Environmental pollution, age, and airway hyperreactivity are also the risk factors. Destruction of the lung parenchyma leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil (Fig. 1).

2) Candidate Gene-Association Studies for the Development of COPD

a) The genes related to the protease-antiprotease imbalances

There are two major hypotheses on the cause of COPD and emphysema, such as the protease-antiprotease hypothesis and the oxidant-antioxidant hypothesis (5, 6). It is well known that the Z alpha (1)—antitrypsin homozygote is predisposed to developing early onset basal, panacinar emphy-
Figure 1. The risk factors for the development of COPD.

Figure 2. Hypothesis of genetic susceptibility to COPD (6).

c) Xenobiotic enzymes and genetics of COPD

Each puff of a cigarette contains $10^{17}$ free radicals and about 4000 substrates including carcinogenic agents and other possible causative agents of COPD such as volatile aldehydes and hydrogen cyanide. Thus, defects in the detoxification of these reactive species may predispose smokers to airflow obstruction and emphysema. It has been suggested that genetic polymorphisms of cytochrome P450, microsomal epoxide hydrolase (mEPHX) are associated with emphysema or COPD (18-20). The genetic polymorphism of exon 5 of smokers with glutathione S-transferase P1 (GSTP1) is associated with the development of COPD in smokers (3). There is growing evidence for the role of xenobiotics and antioxidant imbalance in the pathogenesis of airflow obstruction, which is supported by association studies between COPD and variants in epoxide hydrolase and GSTs that detoxify free radicals and other tobacco products (10-14).

d) Other genes associated with the genetic predisposition to COPD

Because airway obstruction is due to both loss of lung elastic recoil and inflammatory narrowing of peripheral airways, genetic polymorphisms that affect either process could be involved. It has been suggested that genetic polymorphisms of tumour necrosis factor-α, interleukin-13 (IL-13) gene promoter, and Vitamin D binding protein gene are associated with emphysema or COPD (21-23).

3) The Pathologic Relationship between Respiratory Illness in Childhood and Chronic Airflow Obstruction in Adulthood. —Adenoviral Latent Infection Thytypohthesis—

It has been suggested that respiratory illness in childhood might cause chronic air-flow obstruction in adulthood. Hogg
JC and colleagues have suggested an association between latent adenoviral infection with expression of the adenoviral E1A gene and COPD (24, 25). The present study focuses on how the adenoviral E1A gene could alter expression of growth factors by human bronchial epithelial (HBE) cells. The data show that connective tissue growth factor (CTGF) and transforming growth factor (TGF)-beta1 mRNA and protein expression were upregulated in E1A-positive HBE cells. The latent infection of epithelial cells by adenovirus E1A could contribute to airway remodeling in COPD by the viral E1A gene, inducing TGF-beta1 and CTGF expression and shifting cells to a more mesenchymal phenotype.

### Conclusion and Implication

Chronic obstructive pulmonary disease (COPD) is the collective term describing two separate chronic lung disease diseases: emphysema and chronic bronchitis. Results of many studies have suggested that the genetic susceptibility to COPD is dependent on the action of several gene polymorphisms operating in concert. Polymorphisms in an individual gene may impart only a small relative risk of COPD, and it is likely that the cumulative effect of many polymorphisms will be important in its pathogenesis. Before these associations are generally accepted, they must be subjected to scrutiny with further association studies in terms of ethnicity and COPD phenotypes.

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### References