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 propor-

tion 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.

sema (7). In patients with the secretory defect of alpha (1)—antitrypsin, the lung tissue is under uncontrolled proteolytic attack from neutrophil elastase, culminating in alveolar destruction (8-12). The mouse metalloelastase knock-out studies implicate this enzyme as a key mediator in the pathology associated with cigarette smoke-induced emphysema (13, 14). There is also associative evidence from human genetic and animal studies suggesting a pathological link with other MMPs. The polymorphism of alpha-1-antichymotrypsin (AACT) and tissue inhibitor of metalloproteinases-2 (TIMP-2) gene polymorphisms may be associated with individual susceptibility to the development of COPD. The AACT/Ala-15 genotype may be less protective against smoking injury.

b) The genes related to the oxidant-antioxidant imbalance

Oxidative stress is believed to play an important role in the pathogenesis of smoking-induced COPD. The second hypothesis is the oxidant-antioxidant theory, which proposes that oxidant stress and reactive oxygen species (ROS), resulting from an oxidant/antioxidant imbalance, have important consequences for the pathogenesis of COPD. These include oxidative inactivation of antiproteases, alveolar epithelial injury, increased sequestration of neutrophils in the pulmonary microvasculature, and gene expression of proinflammatory mediators. Several studies have provided supportive evidence of a role for reactive oxygen species (ROS) released from circulating neutrophils and the development of airflow limitation. Thus, the presence of oxidative stress may have important consequences for the pathogenesis of COPD. Number of studies have been done on the identification of genes that predispose to the development of COPD.

Heme oxygenase-1 (HO-1) plays a protective role as an antioxidant in the lung. The length of the (GT)_n repeat in the 5'-flanking region of human HO-1 gene polymorphism is associated with susceptibility to COPD (15). The polymorphisms of antioxidant genes glutathione S-transferase M1 (GSTM1) and GSTP1 are reported to be associated with susceptibility to an accelerated decline of lung function in smokers (16, 17).

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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 COOD

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 Air-Flow Obstruction in Adulthood. —Adenoviral Latent Infection Thyptohesis—

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)-beta 1 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-beta 1 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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