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EDITORIAL-YRJÖ JAHNSSON FOUNDATION SYMPOSIUM

Smoking and COPD-Mechanisms and Prevention

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The prevalence of COPD is increasing all over the world, and it develops in only a proportion of smokers for reasons that are still largely unclear. Due to the importance but also the poor understanding of many aspects in COPD and smoking behavior, the Yrjö Jahnsson Foundation organized a meeting "Smoking and COPD-Mechanisms and Prevention" which was held in Sannäs, Porvoo, Finland 20–22 August 2008. A total of 70 researchers participated in the meeting including 12 international experts in the field of COPD research. This meeting focused on the many unresolved factors in COPD, such as its genetics, pathogenesis, progression and systemic manifestations; as well as aspects of nicotine addiction and smoking cessation. Both original research and perspectives presented at this conference are contained in this issue of COPD: Journal of Chronic Obstructive Pulmonary Disease.

An increasing number of studies are showing that chronic bronchitis is associated with increased mortality, co-morbidities and increased risk for development of COPD (1–4). A study in this Issue investigated whether there is a safe long-term level of smoking, but could not find a threshold. This study was conducted on a large Finnish twin cohort including over 21,000 individuals who were followed from 1975 to 1990. The investigators found that smoking co-twins had a significantly increased likelihood for chronic bronchitis compared to their never-smoking co-twins (5). This same group previously extensively investigated the genetic epidemiology of smoking behavior, and their findings are reviewed by Kaprio and coworkers (6).

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The studies clearly reveal a major genetic contribution to smoking behavior. A large Finnish twin cohort from 1974 and a U.S.-Australian collaboration, the Nicotine Addiction Genetics (NAG) study, delved deeper into this complex area and detected significant linkage in two different data sets, a finding that is now being followed-up in an independent case-control study. Recent studies have consistently implicated the nicotine receptor gene complex on chromosome 15 (7). However, this chromosome accounts only for a small fraction of the genetic risk of nicotine dependence. It is obvious that larger studies are still needed since nicotine dependence and success in smoking cessation are both complex and highly dependent on multiple environmental factors including the availability of tobacco, its marketing, socioeconomic conditions, and religious beliefs. Apparently these factors are more important than the impact of a single gene in determining nicotine dependence.

Cigarette addiction is a complex phenomenon as are the several mechanisms underlying it. The multiple facets of the addiction are discussed in the review of West (8) culminating in a more comprehensive set of principles to help smokers overcome their addiction. Berlin's (9) review of the pharmacological therapies for smoking cessation shows that nicotine replacement therapies are effective, but their combination with other drugs, mainly bupropion, is more effective than is mono therapy. There are, however, multiple uncertainties in successful quitting, such as the optimal length of nicotine replacement therapy and the optimum timing of use of combination therapies.

The prevalence of COPD has been estimated to vary between 4–10% in adult populations, 12% for men and 8.5% for women (10) but there seems to be considerable underdiagnosis. A large postal survey, Obstructive Lung Disease in Northern Sweden (OLIN), on nearly 6000 subjects conducted by Lundback and coworkers (11) confirmed the extent of underdiagnosis of COPD in Scandinavia. They followed a cohort of 266 COPD patients for over 20 years, and found surprisingly that many patients with severe COPD were still alive after 20 years, suggesting a substantial difference between population based and hospital recruited COPD cohorts. Laitinen and coworkers (12) developed multiple indicators for predicting and validating COPD phenotypes and disease progression using a cohort of over 800 COPD patients from hospital recruited subjects in

Southern Finland. The baseline data from this cohort revealed clear gender related differences: women suffered more symptoms and more significant impairment of gas exchange than men, while men exhibited higher numbers of systemic manifestations. The basis for these gender related differences in various COPD phenotypes and disease progression remains poorly understood.

The strong association of COPD with multiple co-morbidities suggests that COPD is a "systemic inflammatory disease" (13). The Icelandic group of Gislason (14) investigated 758 randomly selected men and women in Reykjavik, and noted that 33% reported having hypertension and, in agreement with earlier studies, had higher BMI and higher CRP levels. They also had lower values of FEV1 than predicted after adjusting for age, BMI, smoking and CRP. These results emphasize the close association of numerous age-related diseases, which may make independent contributions to the development of airway obstruction.

Typical features in COPD include airway obstruction with peripheral airway fibrosis, however fibrotic lesions can be detected in the parenchyma of the COPD lung as well. Transforming growth factor beta (TGF-β) is a potent modulator of the extracellular matrix (15) and may possibly explain part of these pathological alterations in the lung, Recent studies have pointed to reduced TGF-β and TGF-β receptor expression in COPD lungs while local areas of the lungs reveal increased expression of TGF-β compared to healthy smokers (16). The findings of the study conducted by (17) Leppäranta, Koli and coworkers, reported in this issue, address this complex topic. In their study, Smad2 phosphorylation was used as an indicator of TGF-β signaling and they found evidence that TGF-β signaling activity indeed differs in various parts of the COPD lung. A disturbance in the balance of this pathway in turn probably contributes both to the development of emphysema and small airway fibrosis in the same lung.

Brusselle and collegues (18) from Ghent reviewed the significance of dendritic cells in COPD. These cells are professional antigen presenting cells, originating from the hematopoietic system. They can be divided into two main populations: myeloid DCs (mDCs) originating from myeloid precursors and plasmacytoid DCs (pDCs). There are different numbers of pulmonary dendritic cells in COPD patients, smokers and non-smokers, with different patterns of expression in both central and peripheral airways.

Cigarette smoke modulates dendritic cell function, alters dendritic cell numbers and alters dendritic cell function in experimental models (19). This suggests a potentially important role for dendritic cells in the pathogenesis of COPD, which is still largely undefined. The molecular mechanisms of abnormal inflammation in COPD have been widely investigated but are still poorly understood. Rahman and coworkers (20) found that an imbalance of histone acetylases/deacetylases can trigger transcription of a large number of inflammatory genes in the lung. Cigarette smoke and oxidants inhibit the activity of histone deacetylases, one of those enzymes being Sirtuin1, which has recently been shown to be downregulated in subjects with COPD (21).

In agreement with the ROS-mediated hypothesis, it would be logical to hope that compounds with antioxidant characteristics would play a regulatory role in histone acetelylase/deacetylase homeostasis, and would be efficacious in reversing smoke-induced oxidant/antioxidant imbalance in the lung. In fact, experimental models have detected many of these beneficial effects *in vivo*, but we still lack conclusive evidence of an effective redox modulatory compound/antioxidant that would have meaningful effects in human COPD.

Since one of the major antioxidant systems of human lung is the extracellular form of superoxide dismutase, ECSOD (22), it is likely that a modifier or mimic of this system would be effective in blocking some of the oxidant steps in the pathogenesis of COPD. Recent genetic studies, as reviewed by Oberley-Deegan et al. (23), show that ECSOD plays a unique role in protecting against the development of COPD, suggesting that genetic variations in the expression of this enzyme may be part of the explanation as to why some smokers develop COPD while others do not.

A new way to study COPD and its development/pathogenesis is the so-called non-hypothesis driven proteomic/metabolimic/libidomic approach to find new biomarkers for COPD. While it has been become increasingly clear that COPD is a complex disease with systemic manifestations, it is also apparent that most markers including markers of oxidant and protease burden are not specific for COPD (24). To date only a few studies have focused on proteomics in COPD using either lung tissue (25), sputum (26–28) or bronchoalveolar lavage (29). So far, the results of these studies have been variable and thus a more comprehensive understanding of the advantages and limitations of these methodologies in COPD is required. These problems have been critically reviewed in this issue of COPD: Journal of Chronic Obstructive Pulmonary Disease by the group of R Djukanovic and coworkers (30).

COPD represents one of the most challenging worldwide epidemics today. The Yrjö Jahnsson Symposium, summarized by original research and critical perspectives included in this issue, illustrates only a small part of the research going on in the field of COPD, and highlights some of the international efforts/collaborations, which are important for progress in finding a way to control this disease.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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