Epithelial Cell and Lung Cancer: Introduction

Christophe Doms^a Peter J. Barnes^b

^aDepartment of Pulmonology, University Hospitals Leuven, Leuven, Belgium; ^bNational Heart and Lung Institute, Imperial College, London, UK

In the first half of 2011 a new thematic review series in *Respiration* will focus on epithelial cell and lung cancer. Many studies have recently highlighted the potential association between chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), lung transplantation, glucose metabolism and lung cancer, but this raises intriguing scientific questions as it is not yet fully understood. This series will outline the epidemiology, risk factors and potential pathogenesis of the nexus between lung cancer and COPD, IPF, lung transplantation, and glucose metabolism.

COPD is associated with an increased risk of developing lung cancer after adjusting for confounders including smoking. An FEV₁ <70% of predicted was associated with a >2-fold increase in the risk for lung cancer in men and an almost 4-fold increase in women [1]. A 4.7-fold increase in the risk of lung cancer was observed in a large dataset of patients with IPF [2]. Dickson et al. observed that 6.9% of lung transplant recipients developed lung cancer in the native lung, while no lung cancer was observed in matched bilateral lung transplant recipients [3]. Recent findings show that epithelial cell signaling pathways are responsible for both tumor cell proliferation and the regulation of metabolic pathways in lung cancer [4].

Although cigarette smoking is considered the main risk factor for lung cancer, others, such as chronic inflammation and oxidative stress, have been identified. Chronic inflammation and oxidative stress also play a crucial role in chronic lung diseases such as COPD and IPF. Furthermore, post-transplant immunosuppressive treatment is often considered a risk factor for lung cancer.

Recently, new data on (epi)genetic mechanisms have made the link between lung cancer and other respiratory diseases (such as COPD and IPF) or glucose metabolism. The transcription factor NF- κ B has been linked to COPD and lung cancer through its role in inflammation, cell proliferation and apoptosis [5]. Epigenetic modifications are molecular mechanisms that regulate gene expression without changing the DNA sequence; DNA methylation, histone acetylation and microRNA expression have received most attention with regard to tumorigenesis and COPD [6, 7]. The association between single nucleotide polymorphism in the α 5 subunit of the nicotinic acetylcholine receptor subunit genes (nAChR) on chromosome 15q25 and lung cancer may be confounded by COPD [8]. It has been observed that nAChR is causally involved in alveolar destruction as a potentially shared pathogenic mechanism in lung cancer and COPD [9]. Activation of the Wnt- β -catenin pathway contributes to tumor cell

proliferation, or epithelial cell injury and impaired epithelial-mesenchymal cross talk in IPF [10]. Activation of growth factor receptors leads to both tyrosine kinase signaling and PI3K/Akt/mTOR signaling, which stimulates the transcription of glucose transporters for glucose uptake and glycolytic enzymes in cancer cells [4].

A better understanding of the links between cellular and molecular mechanisms underlying the causal relationship between COPD or IPF and lung cancer, as well as the relationship between cellular metabolism and growth may ultimately lead to novel and/or better treatments for COPD, IPF and lung cancer in the near future.

References

- 1 Wasswa-Kintu S, Gan WQ, Man SE, et al: Relationship between reduced forced expiratory volume in 1 second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax* 2005;60:570–575.
- 2 Le Jeune I, Gribbin J, West J, et al: The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Respir Med* 2007;101:2534–2540.
- 3 Dickson RP, Davis RD, Rea JB, Palmer SM: High frequency of bronchogenic carcinoma after single-lung transplantation. *J Heart Lung Transplant* 2006;25:1297–1301.
- 4 Vander Heiden M, Cantley L, Thompson C: Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009;324:1029–1033.
- 5 Yao H, Rahman I: Current concepts on the role of inflammation in COPD and lung cancer. *Curr Opin Pharmacol* 2009;9:375–383.
- 6 Pfeifer GP, Rauch TA: DNA methylation patterns in lung carcinomas. *Semin Cancer Biol* 2009;19:181–187.
- 7 Adcock IM, Tsaprouni L, Bhavsar P, Ito K: Epigenetic regulation of airway inflammation. *Curr Opin Immunol* 2007;19:694–700.
- 8 Young RP, Hopkins RJ, Hay BA, et al: Lung cancer gene associated with COPD: triple whammy or possible confounding effect? *Eur Respir J* 2008;32:1158–1164.
- 9 Lambrechts D, Buysschaert I, Zanen P, et al: The 15q24/25 susceptibility variant for lung cancer and chronic obstructive pulmonary disease is associated with emphysema. *Am J Respir Crit Care Med* 2010;181:486–493.
- 10 Königshoff M, Balsara N, Pfaff EM, et al: Functional Wnt signaling is increased in idiopathic pulmonary fibrosis. *PLoS One* 2008;3:e2142.