LINK TO ORIGINAL ARTICLE

Mechanistic links between COPD and lung cancer: a role of microRNA let-7?

Jae Il Shin and Guy G. Brusselle

In a recent article (Mechanistic links between COPD and lung cancer. *Nature Rev. Cancer* **13**, 233–245 (2013))[1], McGarry Houghton reviewed the association between the presence of chronic obstructive pulmonary disease (COPD) and the development of lung cancer and suggested that genetic and epigenetic changes, inflammation and associated cytokines, smoking, alterations to cell cycle regulation and the presence of specific proteinases produced by immune cells and other stromal cells could be involved in this association. However, even though the review provided an entire and holistic view of this clinically relevant subject, we would like to add microRNAs (miRNAs) and especially the miRNA let-7c as an important pathogenic link between COPD and lung cancer.

Pottelberge *et al.*[2] recently reported that let-7c was significantly reduced among 627 miRNAs in the sputum of patients with COPD who currently smoke compared with never smokers. The decreased expression of let-7c was associated with an increased expression of soluble tumour necrosis factor receptor 2 (TNFR2): *TNFR2* mRNA is a predicted target of let-7c and is implicated in COPD pathogenesis. Using *in situ* hybridization, let-7c expression was mainly located in sputum macrophages and bronchial airway epithelial cells, and there was also a correlation between the level of let-7c and forced expiratory volume in 1 second (FEV_1)[2].

In lung cancer, let-7c is also a tumour suppressor[3,4]. Wang *et al.*[3] reported that let-7c can significantly inhibit the proliferation of lung adenocarcinoma cells *in vitro* and *in vivo*. Moreover, Zhao *et al.*[4] showed a significant association between low levels of let-7c expression and metastasis, venous invasion, advanced tumour, node, metastasis (TNM) stages and poor survival of patients with non-small-cell lung cancer (NSCLC). Importantly, the inhibition of let-7c in NSCLC cells that had low metastatic potential promoted their motility and invasion. These results suggest that decreased let-7c expression could be important in the pathogenetic link between COPD and lung cancer.

MRX34 is the first miRNA mimic to enter Phase I clinical trials[5], and double-stranded let-7 mimics have also been investigated as a means of replenishing this miRNA in mouse models of cancer[6,7]. Considering the fact that COPD influences the risk of lung cancer independently of tobacco use[8], targeting let-7c could be one of the potential therapeutic strategies for treating COPD and lung cancer. However, the efficacy and safety of miRNA mimics still need to be elucidated[5].

Jae Il Shin is at the Department of Pediatrics, Yonsei University College of Medicine, 120–752,CPO BOX 8044, Seoul, Korea.

Guy G. Brusselle is at the Department of Respiratory Medicine, Ghent University Hospital, B-9000 Ghent, Belgium; and the Departments of Epidemiology and Respiratory Medicine, Erasmus MC Rotterdam, 3000 CA Rotterdam, the Netherlands.

Correspondence to J.I.S.
e-mail shinji@yuhs.ac

doi: 10.1038/nrc3477-c1

1. Houghton, A. M. Mechanistic links between COPD and lung cancer. *Nature Rev. Cancer* **13**, 233–245 (2013).
2. Pottelberge, G. R. *et al.* MicroRNA expression in induced sputum of smokers and patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **183**, 898–906 (2011).
3. Wang, P. Y. *et al.* Let-7c inhibits A549 cell proliferation through oncogenic TRIB2 related factors. *FEBS Lett.* **587**, 2675–2681 (2013).
4. Zhao, B. *et al.* MicroRNA let-7c inhibits migration and invasion of human non-small cell lung cancer by targeting ITGB3 and MAP4K3. *Cancer Lett.* http://dx.doi.org/10.1016/j.canlet.2013.08.030 (2013).
5. Bouchie, A. First microRNA mimic enters clinic. *Nature Biotechnol.* **31**, 577 (2013).
6. Trang, P. *et al.* Regression of murine lung tumors by the let-7 microRNA. *Oncogene* **29**, 1580–1587 (2010).
7. Barh, D. *et al.* MicroRNA let-7: an emerging next-generation cancer therapeutic. *Curr. Oncol.* **17**, 70–80 (2010).
8. Young, R. P. *et al.* COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. *Eur. Respir. J.* **34**, 380–386 (2009).

Competing interests statement
The authors declare no competing interests.