

# DNA methylation profiling of non-small cell lung cancer reveals a COPD-driven immune-related signature

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## IMPLICATIONS OF A NOVEL IMMUNE-RELATED SIGNATURE IN COPD-ASSOCIATED NON-SMALL CELL LUNG CANCER

Lung cancer is the commonest fatal malignancy worldwide in both men and women, accounting for >1.3 million deaths each year. The mean time from diagnosis to death is 18 months, new paradigms are urgently needed for treatment and early diagnosis. In cigarette smokers, airways obstruction is a greater risk factor for lung cancer than age or smoking history, and the risk for lung cancer increased in proportion to the degree of airways obstruction.<sup>1</sup> In a general population, impaired lung function and chronic mucus hypersecretion were significant predictors of death from lung cancer, even after adjusting for smoking.<sup>2</sup> In patients with COPD, active inflammation evidenced by elevated levels of C reactive protein, fibrinogen and leucocytes is associated with a fourfold risk of lung cancer. Interestingly, all three major phenotypes of COPD—chronic bronchitis, airway obstruction and emphysema—have been associated with an increased incidence of lung cancer, while this requires further investigation, it suggests that there may be specific inflammatory phenotypes driving the induction of lung cancer.

The work by Wauters and colleagues starts to address this hypothesis, providing further evidence for the link between COPD and lung cancer and novel insights into how lung tumours of patients with COPD differ from those of non-COPD patients.<sup>3</sup> The patient population was well phenotyped and adjacent non-malignant lung tissue was collected for each tumour sample, allowing correction for inter-individual epigenetic variation due to ageing and smoking. The work describes the presence of a specific tumour micro-environment in COPD-associated non-small cell lung cancer (NSCLC),

characterised by reduced immune cell infiltration. This may further phenotype NSCLC and have implications for the treatment of both COPD and lung cancer. Wauters and colleagues examined the genome-wide methylation profile in paired tumours and adjacent tissues from 49 NSCLC surgical resections and identified two subgroups dependent on COPD status. Their unbiased DNA methylation profiling of NSCLC in patients with concomitant COPD demonstrated a characteristic immune-related signature by contrast to lung cancer from non-COPD patients. In the tissue adjacent to the NSCLC from COPD versus non-COPD patients, no such difference was observed. Stratification for COPD status revealed that there was hypermethylation of immune genes in COPD-associated NSCLC. This was predominantly due to hypermethylation of immune genes involved in the innate defence response (*AGER*), lung dendritic cell trafficking (*CCRL2*) and lymphocyte migration (*SIP1*) in tumour cells. The higher methylation status of such genes resulted in reduced infiltration of CD3-positive and CD4-positive immune cells in the tumour microenvironment. Reduced CD4-positive cells suggests that there will be reduced THelper cells in COPD tumours. However, no significant differences were observed for the CD68 macrophage-specific marker, suggesting that macrophage recruitment is unaffected.

These findings are in surprising contrast to the expression of T-cell substrates in patients with COPD, where T-cell markers are generally upregulated. In the submucosa of mild/moderate COPD, the number of CD3+, CD8+ and CD68+ cells is increased as well as numbers of activated T cells (both CD4 and CD8) and macrophages. In the submucosa of *severe* COPD, the number of CD3+, CD8+ and activated CD3+ coexpressing CCR5 receptor is decreased. The number of CD68+ cells remains elevated.<sup>4</sup> Nonetheless, the immune system of patients with COPD is dysfunctional, driving chronic inflammation and predisposing to infections and the immune system in patients with COPD may not be

capable of mounting an effective immune response against the tumour. However, the downregulation of markers for TReg cells suggests that COPD tumours may be less dependent on immunosuppression. The fact that hypermethylation of immune genes (with associated decrease in immune cell infiltration) occurs in COPD tumours and not to such an extent in the surrounding tissue suggests that hypermethylation occurs early in tumour development. Further work is required to define the exact mechanisms. When does hypermethylation occur? Bronchial hyperplasia and squamous metaplasia are reversible preneoplastic lesions seen in COPD and may be induced by pro-inflammatory cytokines. Potentially immune gene hypermethylation may occur later. It would be interesting to examine carcinoma *in situ* to investigate whether hypermethylation of immune genes is an early marker of lung carcinogenesis.

This work suggests an NSCLC subtype characterised by reduced immune cell infiltration and associated with COPD status. It is unknown whether this is a specific phenotype either in terms of COPD or lung cancer. Limited evidence suggests that the most common histological subtype in GOLD stage I is adenocarcinoma and squamous cell carcinoma in GOLD stages II and III.<sup>5</sup> This differential association may be due to the underlying pathogenetic inflammatory mechanisms. Interestingly (though the numbers are small) in this study, mainly GOLD stage I and II, the adenocarcinoma histological subtype does not obviously predominate, though in all likelihood this requires further investigation.

In breast and colon cancer, subtypes characterised by differential expression of immune response genes are predictors of treatment response and survival in other cancers. The same may be true for NSCLC. COPD status or reduced immune cell infiltration may be a predictive biomarker for the effectiveness of standard chemotherapy as well as novel therapeutic agents. Novel NSCLC treatment strategies should take this into account. Cancer immunotherapy to boost host immune antitumour responses is now emerging as an exciting therapeutic strategy. When testing cancer immunotherapies, for example, the anti-PD-1 therapy, nivolumab, in NSCLC, COPD status (in the light of the findings described by Wauters *et al*<sup>3</sup>) might be an important factor determining efficacy. Furthermore, it also suggests the possibility that

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immunomodulatory strategies to treat COPD may reduce the risk of lung cancer. Systemic corticosteroid use has been shown to influence DNA methylation in patients with COPD. Furthermore, a small study has shown that inhaled corticosteroids may reduce the incidence of lung cancer in patients with COPD.<sup>6</sup> Further studies are required to examine the effects of ICS/immunomodulation on immune gene hypermethylation and development of lung cancer in patients with COPD.

**Competing interests** None declared.

**Provenance and peer review** Commissioned; internally peer reviewed.



**To cite** Sethi T. *Thorax* 2015;**70**:1110–1111.



► <http://dx.doi.org/10.1136/thoraxjnl-2015-207288>

*Thorax* 2015;**70**:1110–1111.  
doi:10.1136/thoraxjnl-2015-207535

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