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Mitochondrial-Related Gene Expression and Macrophage Signatures in Non-Small Cell Lung Cancer, Including Patients with Emphysema as Co-Morbidity

Ng Kee Kwong F[1,2*], Nicholson AG[1,2], Pavlidis S[1], Adcock IM[1] and Chung KF[1]

[1]*Airways Disease, National Heart and Lung Institute, Imperial College London, London, UK*

[2]*Department of Histopathology, Royal Brompton and Harefield NHS Foundation Trust, London, UK*

***Corresponding author:** Ng Kee Kwong F, Department of Histopathology, Royal Brompton and Harefield NHS Trust, Sydney Street, London, UK, Tel: +44-0-20-7352 8121; E-mail: f.ng-kee-kwong@imperial.ac.uk; fkwong270@gmail.com

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Abstract

Objective: Our aim is to determine whether mitochondrial dysfunction is a contributing factor to the increased risk of non-small cell lung carcinoma (NSCLC) in COPD patients.

Methods: The clinical relevance of mitochondrial-related gene expression in lung cancer was determined using transcriptomic data from more than 1000 human NSCLC samples. Immunohistochemistry was then used to study cell type specific expression of the relevant mitochondrial-related protein in normal and cancerous lung tissue. Gene set variation analysis (GSVA) was applied in NSCLC datasets to determine the relative expression of specific macrophage transcriptomic signatures.

Results: The expression of 33 mitochondrial-related genes was correlated with NSCLC patient survival. We studied further the expression of PGAM5 and FUNDC1, which are regulators of mitochondrial degradation (mitophagy). In background lung tissue, PGAM5 and FUNDC1 were only expressed in alveolar macrophages, with highest expression in smokers with emphysema compared to healthy smokers and non-smokers. In cancerous tissue, only the malignant epithelial cells and associated macrophages at the periphery of the cancer, expressed PGAM5 and FUNDC1. PGAM5 was also expressed in pre-neoplastic epithelium (squamous dysplasia and carcinoma *in situ*). There was no difference in expression in cancer tissue between the emphysema, healthy smokers and non-smokers group. Macrophages at the edge of the cancer from emphysema patients had a trend towards higher expression of PGAM5 and FUNDC1 compared to those from the other groups. There was a significant correlation between PGAM5 expression in cancer tissue and 9 out of 49 previously defined macrophage transcriptomic signatures with one (module 22) associated with patient survival ($p<0.05$).

Conclusion: PGAM5 is expressed in pre-neoplastic tissue and NSCLC, but not in normal epithelium. The association between PGAM5 expression and lung cancer outcome may be mediated by the induction of specific macrophage phenotypes.

Keywords: Mitochondrion; Lung cancer; PGAM5; FUNDC1; Macrophage; Patient survival

Introduction

Non-small cell lung carcinoma presents with locally advanced or metastatic disease in 80% of cases [1,2], which accounts for its dismal prognosis at 5 years post-diagnosis [3]. Up to 70% of lung cancer smokers have pre-existing COPD prior to cancer diagnosis [4,5]. The high proportion of patients with COPD developing lung cancer is not solely related to the common risk factor of cigarette smoking. COPD patients are at increased risk of developing lung cancer, irrespective of their smoking history [6-8]. Smokers with airflow obstruction have a five-fold increased risk of lung cancer compared to those with normal lung function [4]. As well as airflow obstruction, emphysema diagnosed on computed tomography (CT) is also an independent risk factor for lung cancer [9,10].

Oxidative stress is a well-recognised driver of carcinogenesis and is present in smokers and COPD patients [11]. The airways of patients with COPD demonstrate an additional increase in oxidative stress, compared to healthy smokers and non-smokers [11]. The production of reactive oxygen species from the mitochondrion is the main source of oxidative stress. The above observation of increased oxidative stress in airway epithelial cells in COPD has been at least partly explained by mitochondrial damage [11]. Under increased oxidative stress, metabolically-active cells may undergo an increase in biogenesis and in degradation of damaged mitochondria within autolysosomes (mitophagy) to replace the old mitochondria which have been damaged by oxidative stress. An imbalance between biogenesis and mitophagy may lead to an excess of dysfunctional mitochondria and increased oxidative stress.

The outcome of lung cancer is known to be related to the phenotype of tumour-associated macrophages (M1 *vs.* M2) and their histological location [12]. However, the traditional division of macrophages into the pro-inflammatory M1 subtype versus the anti-inflammatory M2 subtype has now been superseded by a 'spectrum model' of activated macrophages with at least 49 distinct transcriptomic signatures [13]. Metabolic signatures in macrophages are also linked to their polarisation status [14] and changes in mitochondrial-related protein