Identification and Functional Characterisation of a Genetic Subset of Non-Small Cell Lung Cancer

Claire Louise Mahoney

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Clare College

This dissertation is submitted for the degree of Doctor of Philosophy

DECLARATION

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text. The dissertation does not exceed the word limit set by the Biology Degree Committee.

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ABSTRACT

Non-small cell lung cancer (NSCLC) constitutes ~80% of all lung cancer cases. It is often treated with conventional chemotherapy and has survival rates of only 7% at 5 years. Survival rates improve if it is diagnosed early and can be surgically removed, however over half of all cases are at stage IV at diagnosis. There is a need for new therapeutic targets as well as better detection. This project aimed to functionally characterise a new genetic subset of NSCLC characterised by *LKB1* loss and *KRAS* activation (*LKB1null/KRASmut*). The association of mutations is interesting as the signalling pathways are linked by RHEB. Loss of *LKB1* may lead to over activation of RHEB which inhibits wild type BRAF but not mutant BRAF thus blocking MAPK signalling. NSCLC with *LKB1* mutations may therefore have a general requirement for an activation of the MAPK cascade to overcome suppression of MAPK signalling by RHEB. Following from this, subsequent experiments showed this genetic subset to be sensitive to MEK inhibition and mTOR inhibition. The sensitivity to MEK inhibition is not due to downstream effects on cyclin D1 as reported for melanoma. Comparison of gene expression in this genetic subset compared to other NSCLC cell lines revealed a unique expression signature. Analysis of this signature revealed a metabolic profile dominated by truncation of the citric acid cycle at the pyruvate dehydrogenase reaction. We further characterised these cells using ^{13}C and proton NMR spectroscopy. These data confirmed truncation of the citric acid cycle in the *LKB1/KRAS* mutant subset and suggests this genetic subset of lung cancer creates the Warburg Effect through inactivation of the pyruvate dehydrogenase complex. The NMR spectroscopy highlighted further metabolic changes including the reliance of this subset on both glucose and glutamine metabolism despite the ideal growth conditions of cell culture. The *in vitro* phenotypic data presented in this study make a strong case for these changes being “hard-wired” by the mutation states and thus present further opportunities for their investigation as potential avenues for therapeutic development.

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