**Investigating *Lkb1* loss as novel synthetic vulnerability in *EGFR*-driven lung cancer**

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The discovery of mutations in *EGFR* that drive lung adenocarcinoma growth and confer sensitivity to tyrosine kinase inhibitors (TKIs) has transformed the treatment of lung cancer. Despite these encouraging clinical results, targeted therapies are not curative and the depth and duration of responses to these agents are variable. We know that multiple factors can cause these heterogeneous responses. The genomic landscape of *EGFR*-driven lung adenocarcinomas is complex, and responses to therapy can be influenced by different combinations of genomic alterations that impact tumor fitness and therapeutic sensitivity. We have shown that *Lkb1* inactivation in mouse models of KRAS-driven and EGFR-driven *Trp53*-deficient lung adenocarcinomas had opposite effects. While the loss of *Lkb1* strongly promoted growth of oncogenic KRAS-driven lung tumors, its inactivation reduced EGFR-driven tumor growth. Remarkedly, these effects align with the mutational patterns of these in human lung cancer, where *LKB1* mutations rarely co-occur with *EGFR* mutations. To gain mechanistic insights into this synthetic lethal interaction, we have generated a new conditional lung cancer model based on the inducible expression of EGFRL858R and deletion of *Lkb1* upon activation of a tamoxifen-inducible CreER allele. While *Lkb1* inactivation in established *EGFR*-driven tumors, did not lead to overt tumor regression (assessed by magnetic resonance imaging), we observed increased overall survival in comparison to mice with *Lkb1* wild-type tumors. *Lkb1* wild-type tumors also had increased tumor growth rates. Following *Lkb1* inactivation, morphological changes in some tumors were observed at the histological level, indicative of compromised cell viability. Further histological characterization of these lesions will provide information on the underlying mechanisms driving these morphological changes. To mechanistically dissect why LKB1 is deleterious in EGFR-driven lung adenocarcinomas, we are using multiplexed CRISPR-Cas9-mediated genome editing in our EGFRL858R;p53flox/flox;Cas9 mouse model to establish which LKB1 effectors (AMPK, BRSK, MARK, NUAK, and SIK) are required for the survival EGFR-driven lung cancers. This work will uncover the therapeutic potential of LKB1 pathway inhibition and dissect the downstream effect of the synthetic lethal relationship of LKB1 and oncogenic EGFR.