

 LUNG CANCER

Second chances

Mutually exclusive activating mutations in *KRAS* and epidermal growth factor receptor (*EGFR*) are the most abundant driver mutations in lung adenocarcinomas, the most frequent histological subtype of non-small-cell lung cancer (NSCLC). Yet, mutant *KRAS* has so far proven to be an undruggable target and *EGFR*-selective inhibitors have shown little or no benefit to patients with *KRAS*-driven lung cancer. This has led to the misconception that mutations in *KRAS* confer independence from upstream regulation by *ERBB* family receptor tyrosine kinase (RTK) signalling. However, two groups have now independently established that RTK signalling is active in and necessary for *KRAS*-driven lung tumorigenesis.

To revisit the role of *EGFR*-related signalling in *KRAS*-driven lung cancers, both groups of researchers generated mouse models. Kruspig et al. used an inducible autochthonous mouse model of lung adenocarcinoma driven by endogenously expressed *Kras*^{G12D} combined with modest overexpression of *Myc* (KM mice). Analysis of tumour samples collected from these mice 6 weeks after induction showed increased mRNA expression of *ErbB2*, *ErbB3* and multiple cognate ligands as well as phosphorylated *ERBB* proteins indicative of active signalling. Furthermore, comparison of these early tumours with KM tumours examined after 4–6 months revealed increased expression of phospho-ERK, associated with increased expression of *ERBB* ligands and RTK accessory proteins; a finding suggestive of amplified *ERBB* network signalling sustaining *RAS* pathway activity during *KRAS*-mutant lung cancer progression. In agreement, Moll et al. analysed publicly available datasets of human *KRAS*-mutated lung adenocarcinoma and adjacent normal lung tissue biopsy samples and found mRNA upregulation of *ERBB* RTKs and several of their ligands in the tumour tissue.

The conclusion that the activity of mutated *KRAS* relies on upstream signalling was also reached by Moll et al. by deleting *Egfr* in a mouse model of autochthonous lung cancer driven by *Kras*^{G12D} (KE mice). These mice had reduced tumour cell proliferation and decreased tumour ERK activation 10 weeks after tumour induction, and prolonged survival. Moreover, gene signature analysis of primary alveolar cells isolated from KE mice and induced in vitro demonstrated that deletion of *Egfr* impaired mutant *KRAS* activity.

To confirm that *ERBB* signalling is functionally required for lung tumour development, Kruspig et al. treated KM mice with the pan-*ERBB* inhibitor neratinib. This resulted in decreased activity of *ERBB* RTKs, reduced tumour cell proliferation and increased apoptosis, effects that were not



Credit: Lara Crow/Springer Nature Limited

observed with the *EGFR*-selective inhibitor erlotinib. However, transient *ERBB* inhibition alone failed to improve the overall survival of KM mice but when used in combination with a MEK inhibitor trametinib could extend the survival beyond that attained with MEK blockade alone.

Similarly, Moll et al. found that treatment of mice with the pan-*ERBB* inhibitor afatinib could decrease the growth of tumours formed from human *KRAS*-mutated lung cancer A549 and A427 cell line-derived xenografts as well as a *KRAS*^{G12C}-mutated patient-derived xenograft. In addition, autochthonous lung tumours in a *Kras*^{G12D}-driven mouse model (K mice) were also sensitive to afatinib but not erlotinib or gefitinib (another *EGFR*-selective inhibitor), resulting in reduced tumour burden and importantly decreased ERK activation. Since there was a compensatory mRNA upregulation of non-*EGFR* *ERBB* RTKs in tumours of KE mice 20 weeks after induction leading to a recovery of the tumour proliferation rate, Moll et al. tested the effects of afatinib on tumours generated from *EGFR*-deficient A549 xenografts in mice. This treatment was sufficient to block tumour growth, confirming that afatinib could overcome the tumour escape mechanism mediated by *ERBB* RTKs.

Together these two studies present a strong case for re-evaluating the use of the US Food and Drug Administration (FDA)-approved pan-*ERBB* inhibitors in clinical trials to treat patients with *KRAS*-driven NSCLC.

Anna Dart

because the growth of *PI3K*-p110 α driven breast cancer allografts in mice, which was halted by the ketogenic diet and *BYL-719*, was rescued by the supplementation of exogenous insulin. Similar benefits in response to the ketogenic diet and *PI3K* inhibition using a range of inhibitors were observed in several patient-derived tumour xenograft models or syngeneic tumour allograft models of endometrial adenocarcinoma, bladder cancer and acute myeloid leukaemia (AML), in which *PI3K*-p110 α signalling was driving growth. However, the therapeutic benefit of the ketogenic diet prior to *PI3K* blockade varied across models, and showed adverse effects when given alone in the AML model.

While insight into systemic glucose–insulin feedback will inform clinical practice, caution needs to be taken when translating these findings into a treatment strategy in the clinic.

Ulrike Harjes

ORIGINAL ARTICLE Hopkins, B. D. et al. Suppression of insulin feedback enhances the efficacy of *PI3K* inhibitors. *Nature* <https://doi.org/10.1038/s41586-018-0343-4> (2018)

co-cultured with NS-F10 cells. Similar results were also observed in another pair of subclones isolated from a different DIPG tumour.

In vivo, bulk tumour cells and NS-F10 cells formed tumours that infiltrated the central nervous system more than tumours derived from NS-F8 cells, and mice with NS-F8-derived tumours survived longer. In addition, tumours grown from NS-F8 and NS-F10 co-cultured cells were more infiltrative than those made only of NS-F8 cells; importantly, neither cell population out-competed the other, suggesting that cooperation operates in vivo.

This work examined only two sets of subclones, but provides a rational explanation for why heterogeneity is maintained in DIPG and pGBM. As crucial subclones can be rare in the overall tumour, this study also has implications for tumour profiling studies and therapeutics.

Sarah Seton-Rogers

ORIGINAL ARTICLE Vinci, M. et al. Functional diversity and cooperativity between subclonal populations of pediatric glioblastoma and diffuse intrinsic pontine glioma cells. *Nat. Med.* <https://doi.org/10.1038/s41591-018-0086-7> (2018)