CANCER

A Ras and NF-κB *pas de deux*

Non-small-cell lung cancer (NSCLC) is a leading cause of cancer death worldwide. Small-molecule inhibitors that target epidermal growth factor receptor (EGFR) have shown some clinical success; however, mutations in *KRAS*, which are detected in 20–30% of NSCLC adenocarcinomas, render these therapeutics mostly ineffective. Two reports in *Nature* now demonstrate that nuclear factor-κB (NF-κB) signalling is essential for the survival of cancer cells with mutations in *KRAS*, revealing a potential new pathway for therapeutic intervention.

In addition to mutations in *KRAS*, loss of p53 activity is a frequent event in NSCLCs. Constitutively active $KRAS^{G12D}$ was previously shown to stimulate the NF-κB pathway, whereas wild-type p53 antagonizes NF-κB activity. Jacks and colleagues found that localization of the NF-κB subunit p65 (also known as RELA) in mouse embryonic fibroblasts was not affected by either expression of $KRAS^{G12D}$ or loss of p53. However, expression of $KRAS^{G12D}$ and concomitant loss of p53 caused p65 to accumulate in the nucleus.

Tumour cells from mice that expressed $KRAS^{G12D}$ and lacked p53 (KP mice) exhibited high levels of NF-κB DNA-binding activity; similar observations were made with human NSCLC cell lines. Blocking NF-κB pathway activation through the expression of a dominant-negative mutant of NF-κB inhibitor-α (IκBα; also known as NFKBIA), or knockdown of either p65 or the NF-κB pathway protein NEMO (also known as IKBKG), induced apoptosis in KP cells, but not wild-type cells. These data reveal that the canonical NF-κB pathway is important for the survival of lung cancers with mutations in *KRAS* and *TP53* (which encodes p53). Indeed, the dominant-negative IκBα mutant blocked tumour formation and attenuated the growth of established tumours in KP mice.

A crucial role for NF-κB in cancers that express mutant *KRAS* was also observed by Hahn and colleagues. The authors found that TANK-binding kinase 1 (TBK1; a non-canonical IκB kinase) was required for the survival of human cancer cells that express mutant *KRAS*, as suppression of TBK1 induced apoptosis in these cells. Consistent with previous observations, the selective inhibition of the Ras effector RALB also induced death in *KRAS*-mutant cells.

Gene expression analyses revealed that the *KRAS*-mutant lung cancers show evidence of Ras and NF-κB pathway activation. Indeed, the levels of *NFKBIA* and the NF-κB precursor *NFKB1* were reduced in *KRAS*-mutant cells, which were restored by the suppression of TBK1. Additional experiments found that mutant KRAS and TBK1 were required for the nuclear accumulation of the NF-κB subunit REL, as well as the expression of the anti-apoptotic protein $BCL\text{-}X_L$. Therefore, oncogenic KRAS activates RALB–TBK1 signalling to induce activation of NF-κB and promote cancer cell survival.

Together, the studies from Jacks and colleagues and Hahn and colleagues suggest that the inhibition of the NF-κB pathway might be an effective strategy for treating lung adenocarcinomas that have mutations in KRAS and p53, as well as other cancers that express constitutively active KRAS.

Emily J. Chenette
UCSD–Nature Signaling Gateway

ORIGINAL RESEARCH PAPERS Meylan, E. *et al.* Requirement for NF-κB signalling in a mouse model of lung adenocarcinoma. *Nature* **462**, 104–107 (2009) | Barbie, D. A. *et al.* Systematic RNA interference reveals that oncogenic KRAS-driven cancers require TBK1. *Nature* **462**, 108–112 (2009)