SIGNALLING

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.

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ORIGINAL RESEARCH PAPERS Meylan, E. *et al.* Requirement for NF-κB signalling in a mouse model of lung adenocarcinoma. *Nature* 21 Oct 2009 (doi:10.1038/nature08462) | Barbie, D. A. *et al.* Systematic RNA interference reveals that oncogenic KRAS-driven cancers require TBK1. *Nature* 21 Oct 2009 (doi:10.1038/nature08460)