IN BRIEF

APOPTOSIS

Treatment of *B-RAF* mutant human tumor cells with a MEK inhibitor requires Bim and is enhanced by a BH3 mimetic

Cragg, M. S. *et al. J. Clin. Invest.* 23 Oct 2008 (doi: 10.1172/JCI35437)

MEK–ERK inhibitors have received much attention as potential cancer therapeutic agents but their exact mode of action remains unclear. This study shows that the cytotoxic effect of MEK inhibition in cells that harbour *BRAF* mutations requires the pro-apoptotic BH3-only protein BIM (also known as BCL2L11). In human *BRAF*-mutant, but not wild-type, cells MEK inhibition led to significant apoptosis that was dependent on BIM activation. Apoptosis was further enhanced by the addition of the BH3 mimetic ABT-737, and similar results were observed *in vivo* when cells were grown as subcutaneous tumours in nude mice. Together, these data suggest that the combined administration of a MEK inhibitor and a BH3 mimetic might be an effective and specific therapeutic approach for cancers, such as melanoma, in which *BRAF* mutations are common.

TUMOUR BIOLOGY

The ubiquitin ligase Siah2 regulates tumorigenesis and metastasis by HIF-dependent and -independent pathways

Qi, J. *et al. Proc. Natl Acad. Sci. USA* **105**, 16713–16718 (2008)

The ability of the SIAH2 ubiquitin ligase to regulate HIF1α (hypoxia-inducible factor 1α) stability prompted Qi and colleagues to investigate its role in cancer. By reducing SIAH1 activity in murine melanoma cells using a peptide that prevents association with adaptor proteins, the authors showed that SIAH2 promotes metastasis in a HIF1α-dependent manner. However, by using a dominant negative SIAH2 mutant, they showed that the ability of SIAH2 to promote tumorigenesis is HIF1α independent and is linked to its ability to downregulate levels of Sprouty, an inhibitor of the Ras pathway. Thus, the function of SIAH2 in cancer is tightly associated with its choice of substrate and the authors postulate that understanding the mechanisms dictating SIAH2 substrate preference might provide important insights into key cancer-related processes.

GENE PROFILING

Gene expression in fixed tissues and outcome in hepatocellular carcinoma

Hoshida, Y. *et al. N. Engl. J. Med.* 15 Oct 2008 (doi: 10.1056/NEJMoa0804525)

The routine use of gene profiling in cancer has been limited by the paucity of frozen tissue, but the authors of this study developed a modified method of the complementary DNA-mediated annealing, selection, extension and ligation assay to analyse the expression of 6,000 transcripts from formalin-fixed paraffin-embedded hepatocellular carcinoma tissue samples. This approach allowed them to identify a genetic signature that correlated with late disease recurrence and survival. Importantly, this genetic profile was associated with the surrounding tissue rather than the primary tumour itself, which supported the notion that late recurrences are in fact independently derived tumours. Not only is it hoped that these findings will help identify patients at greatest risk of hepatocellular carcinoma recurrence, but also that this technology might be extended to increase our understanding of other tumour types.