TARGETED THERAPIES

Priming apoptosis

KRAS and the PI3K/AKT/mTOR pathway are frequently dysregulated in cancer, and this pathway represents one of the most critical targets in clinical oncology. However, direct targeting of KRAS has not been successful so far, and inhibition of the PI3K/AKT/mTOR pathway often results in resistance. Finding additional targets that can be blocked in combination with inhibitors of these pathways to induce cell death and promote tumour regression is an approach that has been explored independently by the groups led by Steven Grant and Jeffrey Engelman.

Engelman explains, “to identify potential gene targets that can be blocked in combination with an inhibitor of MEK (an effector protein acting downstream of KRAS) to induce cell death, we used a pooled short-hairpin RNA (shRNA) library and screened 1,200 genes in *KRAS* mutant cancer cells cultured in the

presence and absence of a MEK inhibitor.” This screening process revealed that BCL-XL, which inhibits proapoptotic proteins and prevents them from inducing cell death, was one of the most promising candidates for combination therapy with

MEK inhibitors in *KRAS* mutant cancers. “We found that, although MEK inhibitors alone fail to induce cell death in *KRAS* mutant cancer cells, they may actually prime cells for death by markedly inducing levels of the proapoptotic protein BIM,” says Corcoran, lead author of the study. BIM cannot promote cell death when it is bound to BCL-XL, “however, if cells were given an inhibitor of BCL-XL in combination with a MEK inhibitor, the ability of BCL-XL to bind and inhibit BIM would be blocked, and these increased levels of BIM would be free to promote cell death” continues Corcoran. Indeed, the combination of an inhibitor of BCL-XL and a MEK inhibitor induced marked cell death in most of the *KRAS* mutant cell lines tested and led to tumour regression in five different mouse tumour models of *KRAS* mutant cancers.

Steven Grant and his coauthors also used an shRNA knock-down strategy in human myeloid leukaemia cell lines, and in human xenograft models, to determine the functional significance of proteins whose expression was modified by the dual inhibition of the PI3K/AKT/mTOR pathway and BCL-XL: “the major finding was that PI3K/AKT/mTOR inhibitors markedly downregulated the antiapoptotic

protein MCL1 and synergistically potentiated the lethality of the BCL-XL inhibitor, ABT-737,” explains Grant. The researchers observed that the increased lethality of the combination treatment was mediated by the proapoptotic protein BIM (likely released from BCL-XL) and the AKT target protein GSK3, and that dual inhibition of both BCL-XL and the apoptosis regulator BCL2 was necessary for optimal cell killing.

Both authors hope that this therapeutic strategy could provide clinical benefit for patients with *KRAS* mutant cancer and acute myeloid leukaemia. According to Engelman, a clinical trial of combined BCL-XL and MEK inhibition in patients with *KRAS* mutant cancers is currently under development.

M. Teresa Villanueva

Original articles Corcoran, R. B. *et al.* Synthetic lethal interaction of combined BCL-XL and MEK inhibition promotes tumor regressions in *KRAS* mutant cancer models. *Cancer Cell* doi:10.1016/j.ccr.2012.11.007 | Mohamed, R. *et al.* Dual inhibition of Bcl-2 and Bcl-xL strikingly enhances PI3K inhibition-induced apoptosis in human myeloid leukemia cells through a GSK3- and Bim-dependent mechanism. *Cancer Res.* doi:10.1158/0008-5472