TARGETED THERAPIES

Smart tumor, smarter treatment

Treatment of melanoma has changed drastically with the development of the first inhibitor of BRAF, vemurafenib. *BRAF* is mutated in 70% of patients with melanoma and treatment with vemurafenib has led to significant tumor responses in 80% of these patients. Although with not such high frequency (approximately 10%), *BRAF* is also mutated in colorectal cancers (CRC), however, only 5% of these CRC tumors with mutated *BRAF* respond to vemurafenib.

René Bernards and his colleagues were interested in unravelling the mechanisms of intrinsic resistance of CRC to vemurafenib. To that end, they carried out an RNA interference genetic screen to identify genes that modulate the response of CRC tumor cells to vemurafenib and found that knocking down EGFR with short-hairpin RNA resulted in sensitivity to the drug. This finding suggested that vemurafenib activates EGFR through a feedback mechanism, which results in tumor progression. Indeed, inhibition of EGFR with the tyrosine kinase inhibitor

erlotinib or with the monoclonal antibody cetuximab, also resulted in sensitivity of CRC cells to vemurafenib.

But how does vemurafenib activate EGFR? Further experiments showed how BRAF inhibition leads to inhibition of MEK and ERK kinases, which in turn inhibits CDC25C, an enzyme that binds and dephosphorylates EGFR. Hence, inhibition of CDC25C causes an increase in phosphorylation, and activation, of EGFR.

This study not only demonstrates that combining BRAF and EGFR inhibitors is an option in the treatment of *BRAF* mutant CRCs—in which only standard chemotherapy is effective—but also suggests a role for EGFR as a biomarker in predicting the response to vemurafenib in other tumors.

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Original article Prahallad A. *et al.* Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature* doi:10.1038/nature10868