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CELL SIGNALLING

Even kinase-inactive BRAF is oncogenic

Diverse *BRAF* mutations are detected in a range of cancer types. Mutations that result in RAS-independent activation of BRAF as monomers and dimers, termed 'class 1' and 'class 2' mutations, respectively, are established oncogenes. By contrast, the oncogenic role of 'class 3' mutations was unclear, but has been clarified in two papers published in *Nature*.

"We have used a genetic approach to address a perplexing finding that has intrigued the cancer community for a number of years: the identification of cancers with mutations that result in kinase-inactive (class 3) BRAF isoforms," explains David Santamaria, an author of one of the papers. Kinase-inactivating *BRAF* mutations are more abundant than activating class 1/2 mutations in lung adenocarcinoma, and are commonly found in melanomas and colorectal cancers (CRCs), underscoring their likely importance in tumorigenesis. Santamaria summarizes, "our studies provide, for the first time, genetic evidence demonstrating that kinase-inactive BRAF isoforms are *bona fide* oncogenic drivers."

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Using a range of *in vitro* and *in vivo* models, the authors of the two studies determined that class 3 BRAF mutated proteins have an enhanced capacity to bind RAS and CRAF, leading to CRAF-dependent activation of MEK/ERK, thereby contributing to tumorigenesis. Contrary to class 1/2 mutants, oncogenic signalling by class 3 BRAF mutants is dependent on RAS activation. Accordingly, genetic aberrations that result in RAS activation are mutually exclusive with class 1/2 *BRAF* mutations, whereas they occasionally co-occur with class 3 BRAF mutations. Notably, the predominant mechanism of RAS activation upstream of class 3 BRAF mutants differs between tumours: receptor-tyrosine kinase (RTK) activation in epithelial tumours, such as CRC and lung adenocarcinoma, versus *RAS* or *NF1* alterations in melanoma.

These findings have important implications for treatment selection. In patient-derived xenograft models, carcinomas with class 3 *BRAF* mutations and wild-type *RAS* and *NF1* were sensitive to RTK and/or MEK inhibitors, but not BRAF inhibitors that target class 1 $BRAF^{V600E/K}$ monomers. By contrast, tumour cells with class 3 *BRAF* and *RAS* or *NF1* mutations are unlikely to be sensitive to RTK inhibition, but were shown to be sensitive to MEK inhibitors, *in vitro*.

"Our work and the accompanying data from Yao *et al.* indicates that the nature of the activated RTK will also have to be determined for each patient, in order to select the appropriate RTK inhibitors." Santamaria concludes, "an important question that we are addressing is whether the use of specific CRAF inhibitors could be a therapeutic strategy to treat tumours driven by class 3 *BRAF* mutations."

David Killock

ORIGINAL ARTICLES Nieto, P. *et al.* A Braf kinase-inactive mutant induces lung adenocarcinoma. *Nature* http://dx.doi.org/10.1038/nature23297 (2017) | Yao, Z. *et al.* Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. *Nature* http://dx.doi.org/10.1038/nature23291 (2017)