HIGHLIGHTS

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ONCOGENES

A flying start

The Cancer Genome Project — launched in 1999 by Mike Stratton, Richard Wooster and Andy Futreal to identify new cancer-causing genes — has got off to a promising start, as they report, in *Nature*, the discovery of a new oncogene in human cancer.

In the first stage of a genome-wide screen, the authors have focused on pathways that are known to be deregulated in cancer. *BRAF* is involved in the RAS–RAF–MEK–ERK pathway — RAS is mutated in ~15% of human cancers — so was a prime candidate for analysis. The gene was sequenced from genomic DNA that was isolated from 15 cancer cell lines, three of which — one melanoma and two non-small-cell lung cancers — were shown to contain single-base-pair substitutions. An extensive screen of 530 cancer cell lines followed this initial result, and revealed that 43, from a range of cancer types, contained a mutation in *BRAF*. Mutations were found exclusively in exons 11 and 15, and analysis of just these two exons from 378 primary cancers or short-term cultures confirmed that *BRAF* was frequently mutated in human cancer.

Although *BRAF* is mutated in a range of cancer types, it is most frequently mutated in melanoma: 59% of the melanoma cancer cell lines and 66% of the melanoma primary cancers investigated contained a mutation. Interestingly, the mutations are not linked to the principal cause of melanoma — ultraviolet (UV)-light irradiation — as the mutations are distinct from the C→T transitions that occur following UV-light-induced thymine dimer formation. Instead, the specificity for melanoma seems to be related to melanocyte biology, as α-melanocyte-stimulating hormone initiates a proliferative signal that operates through the BRAF–ERK kinase cascade.

All of the mutations were found to be in or adjacent to the activation segment of the kinase domain, and analysis of some of the most frequent mutations — V599E, L596E, G463V and G468A — confirmed that the mutations increased the kinase activity of BRAF, resulting in activation of ERK.

But the identification of a gene in cancer with activating mutations does not make an oncogene — the mutations must also be able to cause cancer. The *BRAF* mutants were transfected into NIH-3T3 cells, and were shown to increase transformation efficiency by 70–138-fold — compared with wild-type *BRAF*. These transfected cells could also stimulate tumour growth in nude mice.

So, the Cancer Genome Project is already making progress towards their goal of identifying new oncogenes and tumour suppressors. The frequency with which *BRAF* is mutated in melanoma — a cancer type that is notoriously difficult to treat if not caught early — makes it an important therapeutic target, and the development of kinase inhibitors should soon follow.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Davies, H. *et al.* Mutations in the *BRAF* gene in human cancer. *Nature* 9 Jun 2002 (doi:10.1038/nature00766).