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GENETIC PROFILING

Of mice and men

The use of microarrays to profile genes that are affected in tumorigenesis is now fairly common, yet can we use such data sets from mouse models to identify genetic qualities in human tumours?

Human lung adenocarcinoma is known to be associated with mutations in the oncogene *KRAS*. Tyler Jacks and colleagues have used a mouse model of *Kras*-generated lung cancer, which appears histologically similar to the human disease, to identify a *KRAS* mutation gene signature in human cancers.

First the authors collected data using Affymetrix arrays by comparing *Kras*-driven lung tumours with normal mouse lung, generating a profile of differentially regulated genes. Using a statistical approach, termed Gene Set Enrichment Analysis, they demonstrated that the mouse lung adenocarcinomas were most similar to human lung adenocarcinoma compared with other human lung cancer subtypes or adenocarcinomas from other tissues. However, Jacks and colleagues wanted to take this analysis further and asked if they could identify a *KRAS*-mediated gene profile signature in human lung adenocarcinoma. They show that a *KRAS* signature is not evident when analysing human *KRAS*-mutated compared with *KRAS* wild-type lung adenocarcinomas, but once the mouse *Kras* gene data are added in, the *KRAS* gene signature in the human tumours becomes clear.

However, this only holds true for the genes that are upregulated in response to *Kras* expression in the mouse.

Are the signature genes affected by the level of signalling downstream of *KRAS*? To address this the authors compared a human lung cancer cell line known to have mutant *KRAS* expression with one that expresses wild-type *KRAS*. PCR after reverse transcription of RNA confirmed that 8 out of 9 genes selected from the *KRAS* signature data set showed at least twofold increased expression in cells expressing mutant *KRAS*. Furthermore, comparing the gene profile of the mutant *KRAS* cell line with one from the same cells expressing an RNA-interference construct to target *KRAS* expression showed that a significant number of the signature genes were downregulated. Although these genes are clearly true targets

of the mutant *KRAS* pathway, some genes did not change and several even increased, indicating that other gene changes not regulated by *RAS* might still be important for tumour progression in a *RAS*-mediated context.

Most patients diagnosed with lung adenocarcinoma will die from the disease. The identification of both a valid mouse model for this disease and of a *KRAS* gene signature should help identify novel targets of the *RAS* pathway as potential anticancer targets.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Sweet-Cordero, A. et al. An oncogenic *kras* expression signature identified by cross-species gene expression analysis. *Nature Genet.* 19 Dec 2004 (doi:10.1038/ng1490)

WEB SITE

Tyler Jacks' lab:
<http://web.mit.edu/ccr/labs/jacks/index.html>

