ONCOGENES

# Lineage survival

Immature skin cells depend on the transcription factor MITF for survival, growth and commitment to the melanocyte lineage. Levi Garraway and colleagues now show that MITF is also required for the survival, development and progression of melanoma, and call *MITF* a lineage-survival oncogene.

The authors found that six of eight melanoma cell lines in the NCI60 panel of tumour cell lines had a region of gene amplification on chromosome 3p, and that *MITF* seemed to be the target of this amplification. Examination of human tumours showed that no benign moles had amplification of *MITF*, but 10% of primary melanomas and 21% of metastatic melanomas did. In addition, *MITF* amplification was associated with decreased 5-year survival of patients with metastatic melanoma.

MITF represses cell proliferation by activating inhibitors of the cell cycle, including the tumour suppressor INK4A. INK4A is probably inactivated early in melanoma progression and, indeed, the NCI60 cell lines that contained amplified MITF also contained inactivated INK4A. These cell lines also had activating mutations in BRAF, a vital signalling factor in melanocytes. To examine the role of MITF further, Garraway and colleagues introduced *MITF* and/or activated *BRAF* into melanocytes in which cell-cycle-inhibitor pathways, including the INK4A pathway, had been inactivated, and that were dependent on the addition of certain factors to the cell-culture medium for survival. BRAF activation alone led to some factor-independent growth, but only co-expression of *MITF* and *BRAF* led to factor independence and transformation of the melanocytes. Introduction of dominant-negative *MITF*, or knockdown of *MITF* with short hairpin RNAs, led to growth inhibition of the NCI60 melanoma cell lines.

So, MITF has a crucial lineage-survival function in melanoma, but does it influence a patient's response to chemotherapy? The authors carried out a supervised analysis of the pharmacological data on the NCI60 cell lines and found that cell lines with *MITF* amplification were more resistant to chemotherapeutic agents than those without. When dominant-negative *MITF* was introduced into these cell lines, the chemosensitivity of the cells increased.

The authors conclude that MITF is an essential lineage-survival factor in melanoma cells and might be a useful marker for the selection of appropriate treatment or as a target for therapy.

*Ezzie Hutchinson*


**References and links**

**ORIGINAL RESEARCH PAPER** Garraway, L. A. *et al*. Integrative genomic analyses identify *MITF* as a lineage survival oncogene amplified in malignant melanoma. *Nature* **436**, 117–122 (2005)

**WEB SITE**

**William Seller's lab:** http://research.dfci.harvard.edu/sellerslab/datasets/


## TRIAL WATCH

### Faecal DNA testing for colon cancer

The surgical cure rate for colon cancer is high (up to 90%) when it is detected in its earliest stages, but the popularity of current invasive screening methods is low. Screening for cancer-associated, aberrant DNA methylation in patient blood and faeces has been validated as a potential, non-invasive method of early detection for this disease. However, the currently available markers are not very sensitive or specific. Wei-Dong Chen and colleagues have therefore investigated expanding the repertoire of available methylated-DNA markers for colon cancer by using the methylation status of the non-expressed vimentin gene, *VIM*.

*VIM* has a dense region of CpG dinucleotides in and around its first exon, which are targets for DNA methylation. The authors designed primers to assay this region of DNA for methylation and showed that even though *VIM* is transcriptionally silent in normal mucosal epithelial cells, this DNA region was normally unmethylated. However, in all the cancer cell lines tested this region of *VIM* was 100% methylated.

In most matched pairs of normal and tumour tissue samples from colon cancer patients, methylation of *VIM* exon 1 was specifically present in the cancerous tissues, and was found in both early- and late-stage tumours. Furthermore, the *VIM*-methylation assay could detect colon cancer with a clinical sensitivity of 46% and a specificity of 90%, which compares favourably with the parameters for methylation assays of other individual genes. An existing panel of DNA biomarkers for colon cancer has a combined sensitivity of 52% and a specificity of 94%, so adding this assay to the panel could improve these parameters. The authors will therefore begin using the assay in a multicentre trial that is aimed at identifying an optimal panel of biomarkers for colon cancer detection through faecal DNA testing.


**ORIGINAL RESEARCH PAPER** Chen, W. D. *et al*. Detection in fecal DNA of colon cancer-specific methylation of the nonexpressed vimentin gene. *J. Natl Cancer Inst.* **97**, 1124–1132 (2005)


### Cancer immunization success

The proteins p53 and KRAS are commonly mutated in cancer, and David Carbone and colleagues have now shown that this can be exploited in cancer immunotherapy.

Short peptides were synthesized to correspond to the individual mutations in p53 or KRAS of 39 patients with varying stages of cancer. Mononuclear cells from the peripheral blood of each patient were then pulsed with these peptides, irradiated and returned to the patients intravenously. No toxicity was observed and the results were positive: 26% of the patients produced cytotoxic T lymphocytes (CTLs) against the mutant proteins and 42% of patients showed positive interferon-γ (IFNγ) responses after vaccination. Median survival times of 393 versus 98 days for a positive versus a negative CTL response, and 470 versus 88 days for a positive versus negative IFNγ response were also seen. So, custom-made-peptide vaccination is a feasible, non-toxic method of cancer immunotherapy that is associated with an increase in survival.


**ORIGINAL RESEARCH PAPER** Carbone, D. P. *et al.* Immunization with mutant p53- and K-ras-derived peptides in cancer patients: immune response and clinical outcome. *J. Clin. Oncol.* **23**, 5099–5107 (2005)