normal cell line, they went on to test it on three human tumour cell lines — two with high rates of glycolysis (A549 and PC3) were sensitive to SB204990, whereas one with a low rate of glycolysis (SKOV3) was more resistant. When mice bearing xenografts using these cell lines were treated with SB204990, a cytostatic effect as well as differentiation into glandular mucin-expressing structures was evident in A549 and PC3 xenografts but not SKOV3 xenografts.

The failure of ACLY inhibition to suppress the growth of tumours that do not have high rates of glycolysis indicates that there are alternative lipogenic pathways that tumour cells can use. However, ACLY inhibitors — as well as statins, farnesyl transferase inhibitors and fatty acid synthesis inhibitors — might be useful in combination with other agents to treat advanced tumours, which often have high rates of glycolysis.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Hatzivassiliou, G. *et al*. ATP citrate lyase inhibition can suppress tumor cell growth. *Cancer Cell* **8**, 311–321 (2005)

WEB SITE

Craig Thompson's Lab:
http://www.uphs.upenn.edu/abramson/thompsonLab.html

TUMOUR SUPPRESSORS

Look both ways

The Krüppel-like factor 4 (KLF4) transcription factor can function as a tumour suppressor in various cancer types and as an oncogene in others, including breast cancer. In their *Nature Cell Biology* paper, Daniel Peeper and colleagues have identified some of the molecular mechanisms that explain the Janus-like behaviour of KLF4 in tumorigenesis.

When the authors identified KLF4 as a protein that can bypass cellular senescence induced by oncogenic RAS (RAS^{V12}), they decided to investigate the molecular mechanisms that are at work. They established that KLF4 represses expression of the tumour suppressor p53, but induces expression of the cyclin-dependent-kinase inhibitor p21 (CDKN1A). p53 is a crucial mediator of RAS^{V12}-induced proliferative arrest, so the authors hypothesized that suppression of p53 by KLF4 is probably the means through which KLF4 bypasses senescence. This was confirmed when short hairpin RNAs were used to suppress p53 to levels similar to those achieved by expression of KLF4, which prohibited RAS^{V12}-induced senescence.

How does KLF4 suppress the expression of p53? Northern blots demonstrated that KLF4 downregulates *TP53* mRNA levels, and chromatin immunoprecipitation assays indicated that KLF4 achieves this by directly binding to the *TP53* promoter.

Although KLF4-mediated repression of p53 explains how KLF4 prevents RAS^{V12}-driven arrest, it does not explain the reverse: how RAS^{V12} bypasses KLF4-induced arrest. Indeed, KLF4, similar to most other tumour suppressors, normally triggers cell-cycle arrest. One of the known mitogenic targets of RAS is cyclin D1, and Peeper and colleagues found that RAS^{V12} could not collaborate with KLF4 in stimulating cell proliferation in the absence of cyclin D1 expression, indicating a crucial role for cyclin D1 in this setting.

How does this tie in with the expression of p21, which KLF4 induces? Cyclin D1 neutralizes the p21-induced cell-cycle arrest, so the cells are able to proliferate. In agreement with this hypothesis, p21-null mouse embryonic fibroblasts were unable to arrest in the presence of KLF4. Together, these data indicate that KLF4 is a tumour suppressor that induces cell-cycle arrest by increasing the expression level of p21.

The authors also examined whether the KLF4-mediated repression of p53 could explain the oncogenic behaviour of KLF4 in breast cancer cells. They found that suppressing KLF4 in human breast cancer cell lines restored the expression of p53, which resulted in apoptosis. So, suppression of p53 by KLF4 seems to be important for the survival of breast cancer cells, and this probably explains the oncogenic effect of KLF4 in these cells.

The authors conclude that the systemic targeting of KLF4 would not be desirable, as it would inhibit both the oncogenic and the tumour-suppressor functions of KLF4.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Rowland, B. D., Bernards, R. & Peeper, D. S. The KLF4 tumour supressor is a transcriptional repressor of p53 that acts as a context-dependent oncogene. *Nature Cell Biol*. 23 Oct 2005 (doi 10.1038/ncb1314)