THERAPEUTICS

Dodging anti-angiogenic therapy

The problem with many available cancer therapies is that cancer cells rapidly develop resistance to the treatment because of their genomic instability. Anti-angiogenic therapies have been proposed to avoid this risk as they target wild-type vascular endothelial cells. However, Joanne Yu *et al.*, reporting in the 22 February issue of *Science*, suggest that some tumours can lose responsiveness to anti-angiogenic therapy because of cancer-cell genetic mutations.

How might cancer cells become less responsive to angiogenesis inhibitors? Anti-angiogenic therapies starve the tumour of its oxygen supply, so resistant cells must be able to grow in relatively hypoxic conditions. Cells deficient for the tumour suppressor p53 are known to display this characteristic, so the authors investigated whether p53 status affected tumour sensitivity to an anti-angiogenic therapy, comprising an antibody that blocks vascular endothelial growth factor receptor-2 combined with low-dose chemotherapy. $TP53^{-/-}$ and $TP53^{+/+}$ colorectal cancer cells were injected subcutaneously into immunodeficient mice, and tumour growth was monitored with and without the anti-angiogenic therapy. Although tumour growth slowed following treatment in all tumours, the tumour volume in $TP53^{-/-}$ tumours increased sevenfold after 42 days of treatment, compared with twofold in tumours with intact p53.

So, are the $TP53^{-/-}$ cells selected for when angiogenesis is inhibited? When a 1:1 mix of $TP53^{-/-}$:$TP53^{+/+}$ cells was injected into mice, the number of p53-null cells increased to comprise ~80% of the tumour mass after 35 days.

But how do the remaining $TP53^{+/+}$ cells survive under these hypoxic conditions? Might they shelter in the better oxygenated perivascular part of the tumour? In tumours derived from the 1:1 mix of cells described above, cells located close to blood vessels were fluorescently labelled. Fluorescence-activated cell sorting to separate the cells that were proximal and distal to the vessels, followed by polymerase chain reaction amplification of *TP53*, revealed that the $TP53^{+/+}$ cells preferentially resided close to vessels.

How does p53 status control whether cells can survive anti-angiogenesis treatment? The TUNEL assay, which stains apoptotic and necrotic cells, was used in conjunction with EF5 staining of hypoxic areas to confirm that apoptosis is higher in hypoxic areas of $TP53^{+/+}$ tumours than in $TP53^{-/-}$ tumours. Cancer cells might therefore need p53 to undergo apoptosis following oxygen starvation.

So, genetic instability not only allows tumour cells to dodge therapies aimed directly at them, but also at least some therapies that target their genetically stable milieu. Perhaps combining anti-angiogenic therapies with those that inhibit oncogenic pathways, specifically target hypoxic tumour cells or destroy existing blood vessels, will prevent those crafty cancer cells from staying one step ahead.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Yu, J. L. *et al.* Effect of p53 status on tumor response to antiangiogenic therapy. *Science* **295**, 1526–1528 (2002)

FURTHER READING Marx, J. Obstacle for promising cancer therapy. *Science* **295**, 1444 (2002)

WEB SITE
Robert Kerbel's lab:
http://medbio.utoronto.ca/faculty/kerbel.html