TUMORIGENESIS

Switching roles

The TGF-β signalling pathway has the unusual ability to suppress the initial stages of tumorigenesis, but to promote later stages such as metastasis. An unanswered question, though, is whether the response to TGF-β is dependent on cell type or the specific genetic alterations that induce tumour formation, or whether TGF-β can actually switch roles within a single cell lineage. Lalage Wakefield and colleagues have investigated this, and suggest the latter hypothesis is true.

The group worked with three cell lines that were derived by Fred Miller and colleagues from MCF10A breast epithelial cells (M-I), which are immortal but otherwise normal, and so are non-tumorigenic. Transfection with the *HRAS* oncogene led to the MCF10 AT1k.cl2 (M-II) line, cells from which normally form benign hyperplastic lesions when injected into mice. However, a few of these lesions progress to carcinomas, and these were used to generate the MCF10Ca1h (M-III) line, cells from which form well-differentiated carcinomas, and the MCF10Ca1a.cl1 (M-IV) line, cells from which form poorly differentiated, metastatic carcinomas. All of these cell lines express TGF-β receptors and their proliferation can be inhibited by TGF-β.

So, what effect would inhibiting the pathway have on the four cell lines? The authors transfected them with a dominant-negative TGF-β receptor II, and showed that this could largely block TGF-β signalling for 18 hours. This, in turn, resulted in de-repression of the TGF-β target gene *MYC* and resistance to growth inhibition by TGF-β. Next, these transfected cells were injected into mice, to investigate the effect on tumorigenicity. Although M-I cells were still unable to form tumours — indicating that loss of TGF-β is not sufficient to induce tumour formation — M-II transfected cells formed rapidly growing lesions, to an extent that was statistically significant compared with the M-II control cells. The M-III cell line also changed from one that formed slow-growing tumours on injection into mice, to one that formed fast-growing tumours with a shorter latency on inhibition of the TGF-β signalling pathway. These were of a higher histological grade and were less well differentiated.

By contrast, the tumorigenicity of the M-IV cell line was not affected by inhibition of the TGF-β signalling pathway; injected cells formed tumours at a similar rate and of a similar histology, regardless of the status of the TGF-β pathway. However, metastatic ability was significantly affected. Injection of control M-IV cells into the tail vein of nude mice resulted in lung metastases within 8 weeks in all mice, but only 40% of mice that were injected with transfected cells formed metastases. This indicates that in advanced tumours, the pro-metastatic ability of TGF-β wins out.

So, it seems that TGF-β signalling really can switch from being tumour suppressive to pro-metastatic within a single cell lineage and that this switch can be initiated by a single oncogenic event. This could have implications for therapy that targets TGF-β — whether the signalling pathway needs to be restored or inhibited would depend on the disease stage.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Tang, B. *et al.* TGF-β switches from tumor suppressor to prometastatic factor in a model of breast cancer progression. *J. Clin. Invest.* **112**, 1116–1124 (2003)

FURTHER READING Siegel, P. & Massagué, J. Cystatic and apoptotic actions of TGF-β in homeostasis and cancer. *Nature Rev. Cancer* **3**, 807–820 (2003)

WEB SITE

Lalage Wakefield's lab: http://rex.nci.nih.gov/RESEARCH/basic/lc/LW.HTM

IN BRIEF

ANTISENSE THERAPY

Effects of *MYCN* antisense oligonucleotide administration on tumorigenesis in a murine model of neuroblastoma.

Burkhart, C. A. *et al. J. Natl Cancer Inst.* **95**, 1394–1403 (2003)

One of the main prognostic indicators for neuroblastoma is amplification of the *MYCN* oncogene. Burkhart *et al.* found that inhibition of *MYCN* with antisense oligonucleotides in a human neuroblastoma cell line with amplified *MYCN* decreased expression of the oncogene and decreased tumorigenesis in a mouse model. Investigation of use of *MYCN* antisense in children with neuroblastoma is warranted.

GENOMIC INSTABILITY

The presence of p53 mutations in human osteosarcomas correlates with high levels of genomic instability.

Overholtzer, M. *et al. Proc. Natl Acad. Sci. USA* **100**, 11547–11552 (2003)

One of the pathways that the p53 tumour suppressor regulates is the checkpoint response to DNA damage, so loss of p53 can result in genomic instability. Overholtzer *et al.* show that *TP53* mutations do correlate with high levels of genomic instability in human osteosarcomas. Interestingly, however, amplification of *MDM2* — an upstream inhibitor of p53 — does not increase genomic instability, indicating that inactivation of p53 by different mechanisms has different effects on genome stability.

INFLAMMATION

Loss of collagenase-2 confers increased skin tumor susceptibility to male mice.

Balbin, M. *et al. Nature Genet.* 28 Sept 2003 (doi: 10.1038/ng1249)

Matrix metalloproteinases (MMPs) have an important role in tumour progression. Balbin *et al.* used mice null for *Mmp8* (collagenase-2) — an MMP that is produced by neutrophils during an inflammatory response — to show that Mmp8 protects against development of skin tumours in male mice and female mice with depleted oestrogen. So, inhibitors of MMPs might inhibit not only the tumour promotion effects of the enzymes but also the protective effects, which might explain the lack of success of these agents in clinical trials.

VIRUSES

Characteristics of Hodgkin's lymphoma after infectious mononucleosis.

Hjalgrim, H. *et al. N. Engl. J. Med.* **349**, 1324–1332 (2003)

Epstein–Barr virus (EBV) infection in adolescents can cause infectious mononucleosis, which is associated with an increased risk of developing Hodgkin's lymphoma. Hjalgrim *et al.* followed patients with infectious mononucleosis for incidence of Hodgkin's lymphoma. EBV-positive patients had an increased risk of developing EBV-positive tumours, but not EBV-negative tumours. The authors conclude that the association between infectious-mononucleosis-related EBV infection and EBV-positive Hodgkin's lymphoma is causal.