ONCOGENES

Determining fate

The OCT-3/4 transcription factor is known to determine cell fate — it is required for embryonal stem-cell self renewal and its altered expression results in different cell fates. However, Sharon Gidekel and colleagues now report in *Cancer Cell* that it can also determine the oncogenic potential of germ-cell tumours and could be a useful therapeutic target.

As tumours are thought to be maintained by tumour stem cells, the role of *OCT-3/4* in maintaining the stem-cell fate of germ cells led the authors to investigate whether it might also be expressed in germ-cell tumours. In the adult male, the expression of *OCT-3/4* is restricted to type A spermatogonia, but it was also found to be expressed in all 45 germ-cell tumours that were tested. The expression was particularly high in the pre-malignant cells, so it might contribute to germ-cell neoplasia from an early stage. It was not expressed in any of 182 non-germ-cell tumours.

But what effect does it actually have on tumorigenicity? The authors used several lines of engineered embryonic stem (ES) cells that expressed from 0–150% of wild-type *OCT-3/4*. These were injected subcutaneously into mice and the incidence of tumour formation was determined. Mice that were injected with wild-type cells developed tumours at an incidence of 83%, but this decreased to only 4.3% if *OCT-3/4* was not expressed. Upregulating *OCT-3/4* also increased the proportion of tumours with primitive neural and malignant-appearing tissues, further confirming that it influences cell fate.

Another question was whether OCT-3/4 is required to maintain the malignant phenotype. In one engineered ES cell line, the only copy of OCT-3/4 was under the tetracycline promoter, so could be controlled by doxycycline. When OCT-3/4 expression was switched off after tumours were established, the tumours regressed significantly — in one-third of tumours, the

THERAPEUTICS

Heading for a cure

For many types of brain tumours there is no effective treatment, but promising work by Rosalind A. Segal and colleagues has found that a small molecular antagonist of the chemokine receptor Cxcr4 causes a big headache for brain tumours in mice. As this antagonist already has an encouraging safety profile in humans, they believe it could be considered for immediate evaluation in clinical trials.

Chemokine stromal-cell-derived factor 1α (CXCL12) and its receptor CXCR4 have a crucial role in brain development and are expressed in adult glioblastoma multiforme (GBM), so Segal and colleagues wondered if other types of brain tumours also expressed these proteins. Immunohistochemical staining of human brain tumours identified CXCR4 expression in 9/10 paediatric medulloblastomas and 3/5 anaplastic astrocytomas examined. In addition, published gene-array data from paediatric brain tumours showed that *CXCR4* expression was increased in tumours of glial and neuronal origin. CXCL12 expression in the medulloblastomas was similar to that in GBM, indicating that the CXCR4–CXCL12 interaction might contribute to tumour formation.

CXCR4–CXCL12 signalling is known to cause chemotaxis, increase proliferation and decrease apoptosis, and when Daoy medulloblastoma or U87 GBM cells were stimulated with CXCL12, all of these effects were observed. But addition of AMD 3100 — a small-molecule inhibitor of CXCR4 — to the cultures reduced chemotaxis and proliferation, and blocked serum-free survival. The next step was to determine whether AMD 3100 produced a similar effect *in vivo*. First, they established intracranial xenografts of Daoy and U87 cells that were engineered to express luciferase — which allowed non-invasive imaging of the tumours — then osmotic pumps containing AMD 3100 or PBS were implanted into tumour-bearing mice. Tumour burden was substantially diminished in the AMD-3100-treated animals. Twice-daily subcutaneous injection of AMD 3100 to tumour-bearing animals also reduced tumour growth with no evidence of toxicity in the treated animals.

Interestingly, the antitumour effects of AMD 3100 were different for different tumour types. AMD 3100 increased apoptosis in the GBM tumours, but had no effect on proliferation, whereas apoptosis was increased and proliferation reduced in medulloblastomas. AMD 3100 decreased phosphorylation of ERK1/ERK2 and AKT, downstream effectors of CXCL12, in tumour cells from both animal models, confirming that CXCR4 signalling is impaired.

These are promising results, as the safety of AMD 3100 has already been established in human clinical trials and trials to evaluate its effect on malignant brain tumours could be rapidly established. If successful, CXCR4 antagonists might be useful for treating other types of malignancies that express CXCR4.

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References and links

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FURTHER READING Staller, P. *et al.* Chemokine receptor CXCR4 downregulated by von Hippel-Lindau tumour suppressor pVHL. *Nature* **425**, 307–311 (2003)

WEB SITE

Rosalind Segal's lab:
http://research.dfci.harvard.edu/segallab/