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## THERAPEUTICS

# Swinging the vote for rapamycin

Immunosuppressive drugs are commonly used to prevent immunological graft rejection in organ transplant recipients, but these have many serious side effects, including increasing the patient's risk for developing cancer. Cancer is, in fact, one of the main causes of death in organ transplant recipients. To get around this complication, Markus Guba *et al.* set out on a search for immunosuppressive drugs that have low neoplastic qualities. They report in the February issue of *Nature Medicine* that the immunosuppressant rapamycin (Rapamune) can actually inhibit primary and metastatic tumour growth.

Rapamycin blocks interleukin-2 (IL-2) stimulation of lymphocytes and can prevent graft rejection, but, at present, most transplant patients receive a different immunosuppressive drug — cyclosporin A (CsA) — which acts by inhibiting T-cell proliferation and preventing IL-2 transcription. CsA has, however, been shown to promote cancer progression in animal models. The immune system is known to have an active role in fending off cancer, so how could an immunosuppressant prevent tumour growth?

Guba *et al.* showed that when colorectal adenocarcinoma cells were injected into the hepatic portal vein of mice, rapamycin-treated mice developed fewer and smaller liver metastases than untreated or CsA-treated mice. Rapamycin was also effective in slowing the growth of established tumours in several mouse models. Analysis of tumours by intravital microscopy (see

picture) revealed that rapamycin-treated mice had less tumour-associated vasculature than control or CsA-treated mice. A relatively low, non-cytotoxic dose of rapamycin caused tumours to regress only after they had reached an angiogenesis-dependent stage. So, does this drug inhibit tumour-induced angiogenesis?

It seems that it does, as *in vitro* assays showed that rapamycin treatment reduced expression and secretion of vascular endothelial growth factor (VEGF) by several cancer cell types, whereas CsA has no effect on VEGF production. Rapamycin treatment also reduced VEGF levels in the serum of tumour-bearing mice. The reduction in VEGF production was not enough, however, to account for rapamycin's potent anti-angiogenic effect. So the authors checked to see whether the drug also disrupts VEGF-receptor-mediated stimulation of vascular endothelial cells. Sure enough, they found that it inhibited VEGF-dependent endothelial-cell proliferation and tubule formation in culture. But normal immunosuppressive doses

of the drug did not prevent proliferation of cancer cells in culture, indicating that angiogenic epithelial cells are likely to be an important target.

Although immunosuppressive drugs are generally thought to promote, rather than inhibit, cancer development, rapamycin has been shown to inhibit tumour growth, particularly in mice that lack the PTEN tumour suppressor. Might this effect also have been due to blockage of angiogenesis? Whatever the mechanism, rapamycin might be a safer alternative to CsA therapy in transplant patients, especially those with a predisposition to or a history of cancer.

Kristine Novak

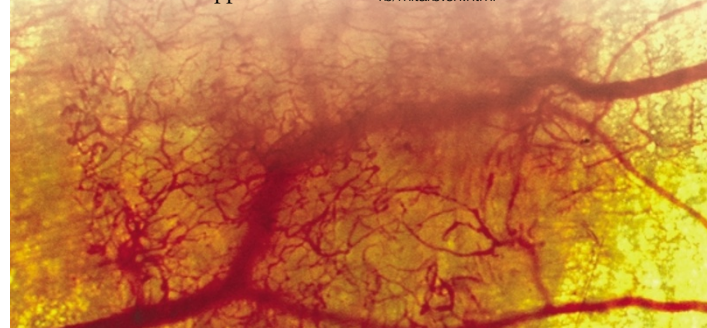
## References and links

**ORIGINAL RESEARCH PAPER** Guba, M. *et al.* Rapamycin inhibits primary and metastatic tumor growth in antiangiogenesis: involvement of vascular endothelial growth factors. *Nature Med.* **8**, 128–135 (2002)

**FURTHER READING** Hojo, M. *et al.* Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature* **397**, 530–534 (1999) | Brooksbank, C. Withdrawal symptoms. *Nature Rev. Cancer* **1**, 6 (2001)

### WEB SITE

Edward Geissler's lab: <http://www.uni-regensburg.de/Fakultaeten/Medizin/Chirurgie/mitarb/mitarb.en.html>



Intravital microscopy of tumour vasculature. Courtesy of Edward Geissler.