HIGHLIGHTS

ANGIOGENESIS

Switch control

Although anti-angiogenic factors such as endostatin can block tumour growth in mice, there have been difficulties in translating these effects to patients. Bergers and colleagues have shown that the makeup of the tumour vasculature varies at different stages of tumour development, so inhibitor efficacy might depend on its application during a specific phase of tumorigenesis.

During their hyperproliferative premalignant stage, tumours produce a variety of factors to cause an 'angiogenic switch' that induces the normally quiescent surrounding tissue to support the formation of new blood vesssels. Bergers *et al*. have been studying the angiogenic switch using the *RIP1Tag2* line of transgenic mice, which develop pancreatic B-cell carcinomas in a multistep pathway. This model allows researchers to test the effects of various therapeutic approaches on distinct stages of tumour development.

In previous studies, the authors observed stage-specific efficacy of various angiogenesis inhibitors. For example, the vascular endothelial growth factor (VEGF) receptor inhibitor SU5416 blocks the angiogenic switch and prevents the growth of premalignant tumours, but does not induce regression of late-stage, well-vascularized tumours (analogous to those of typical Phase III clinical trial participants). This reveals the importance of VEGF signalling during the angiogenic switch and initial tumour growth, but not in large tumours with an established vasculature.

In the May issue of *The Journal of Clinical Investigation*, Bergers *et al*. report the efficacy of broad-specificity receptor inhibitors, such as SU6668 — a small-molecule kinase inhibitor that primarily inhibits signalling through PDGF receptors, but also through VEGF receptors. Although SU6668 slowed early tumour growth in *RIP1Tag2* mice, it was most effective in blocking the growth of late-stage tumours, leading to stable disease. The authors observed that the treated tumours were less vascular, and had a reduction in the association of blood vessels with pericytes — smooth-muscle-related cells that surround and support the vascular endothelium. Pericytes were found to be the only tumour cells that express PDGF receptors, making them an important new target of anti-angiogenesis therapy.

Furthermore, treating the *RIP1Tag2* mice with a combination of a VEGF inhibitor (SU5416) and a PDGF inhibitor (SU6668 or imatinib (Glivec)) was more efficacious against all stages of islet carcinogenesis than either single agent. Combinations such as these might therefore be used to target interdependent cellular constituents of the tumour vasculature in patients — VEGF receptor inhibitors to block vascular-endothelial-cell function and PDGF inhibitors to block pericyte support of blood vessels.

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References and links

ORIGINAL RESEARCH PAPER Bergers, B. *et al*. Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. *J. Clin. Invest*. **111**, 1287–1295 (2003)
FURTHER READING Dancey, J. & Sausville, E. A. Issues and progress with protein kinase inhibitors for cancer treatment. *Nature Rev. Drug Discov.* **2**, 296–313 (2003)
WEB SITE
Gabriele Berger's lab:
http://www.som.ucsf.edu/neuros/faculty/bios/BergersG.htm