ANGIOGENESIS

Barking up the wrong tree?

Vascular endothelial growth factor (VEGF) binds two known receptor tyrosine kinases — FLT1 and FLK1 — but most anti-angiogenic agents that are designed to block VEGF signalling target only FLK1. This is because FLT1 has low tyrosine kinase activity, and its function is poorly understood. A study by Peter Carmeliet and colleagues reveals, however, that FLT1 is a more important therapeutic target than previously believed.

FLT1 binds not only VEGF, but also its homologues, placental growth factor (PGF) and VEGFB. *Flt1*-null mice die during embryogenesis, due to vascular defects, whereas mice expressing *Flt1* that lacks the tyrosine kinase domain survive, indicating that Flt1 might serve solely as a non-signalling 'reservoir' for Vegf. Other studies have shown, however, that antisense-mediated downregulation of Flt1 suppresses tumour angiogenesis.

Carmeliet and colleagues report that an antibody against Flt1 blocks angiogenesis and growth of human epidermoid tumours in nude mice, and was only slightly less effective than anti-Flk1. After 2 weeks of treatment with anti-Flt1, the microdensity of tumour blood vessels decreased by 45%. Anti-Flt1 also stopped the growth and vascularization of Pgf- or Vegf-transduced rat gliomas in nude mice. Surprisingly, anti-Flt1 reduced the symptoms of inflammatory diseases, such as atherosclerotic plaque growth and autoimmune arthritic-joint destruction, in mice.

But what do these diseases have in common with tumour development? Both tumour angiogenesis and inflammatory responses require the mobilization of myeloid progenitors from the bone marrow into the peripheral blood. Carmeliet's group showed that anti-Flt1 reduced this mobilization by 75%, and propose that both Vegf and Pgf are involved in recruiting not only myeloid precursors, but also differentiated leukocytes to inflammatory sites. As anti-Flk1 does not block arthritis or atherosclerosis, Flt1 might be a better therapeutic target, because it could be used to inhibit not only angiogenesis, but also the inflammation that is associated with tumours.

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References and links

ORIGINAL RESEARCH PAPER Luttun, A. *et al.* Revascularization of ischemic tissues by PlGF treatment and inhibition of tumor angiogenesis, arthritis and atherosclerosis by anti-Flt1. *Nature Med.* 1 July 2002 (doi:10.1038/nm731)

THERAPEUTICS

Next in line?

The success of the kinase inhibitor imatinib (Glivec) in the treatment of chronic myelogenous leukaemia — which is caused by the aberrant activity of the BCR–ABL tyrosine kinase — has given much encouragement for the development of other molecularly targeted therapies. As two reports in *Cancer Cell* now indicate, inhibitors of the FLT3 kinase, which is mutated in ~30% of patients with acute myelogenous leukaemia (AML), could be promising candidates for targeted treatment of this disease.

The first study involved the kinase inhibitor CT53518, which is selective for FLT3 and two other kinases, platelet-derived-growth-factor receptor (PDGFR) and KIT, *in vitro*. CT53518 was found to inhibit several different constitutively active *FLT3* mutants that were cloned from patients with AML and expressed in Ba/F3 cells, and also to induce apoptotic cell death in human AML cell lines with mutations in *FLT3*. Encouraged by these observations, Kelly *et al.* tested CT53518 *in vivo* in two mouse models of mutant-FLT3-mediated AML, and found that CT53518 resulted in a significant decrease in disease progression, as assessed by spleen weight and white blood cell (WBC) count, and an increase in survival. Furthermore, CT53518 was shown to have suitable pharmacokinetic and toxicity profiles for clinical use.

The second study, by Weisberg *et al.*, assessed the activity of the kinase inhibitor PKC412 — which targets FLT3, and also the kinases KDR, PDGFR, KIT and protein kinase C — and found it to be highly toxic to Ba/F3 cells that expressed mutant FLT3 receptors from AML patients. And, in a mouse model of mutant-FLT3-mediated leukaemia, PKC412 treatment completely blocked the development of leukaemia, whereas all of the mice in the placebo group developed fatal disease. Moreover, spleen weights and WBC counts were also significantly lower in the treated mice.

Both of these studies strongly support the idea that FLT3 is potentially a good drug target in AML. PKC412 and CT53518 are now being evaluated in clinical trials for AML, and it seems likely that several other FLT3 inhibitors will also be clinically tested. It will be of considerable interest to compare their efficacies and toxicities, as these are likely to be influenced by the non-FLT3 targets of each drug, which might differ significantly.

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ORIGINAL RESEARCH PAPERS Kelly, L. M. *et al.* CT53518, a novel selective FLT3 antagonist for the treatment of acute myelogenous leukemia. *Cancer Cell* **1**, 421–432 (2002) | Weisberg, E. *et al.* Inhibition of mutant FLT3 receptors in leukemia cells by the small-molecule tyrosine kinase inhibitor PKC412. *Cancer Cell* **1**, 433–443 (2002)

FURTHER READING Capdeville, R. *et al.* Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nature Rev. Drug Discov.* **1**, 493–502 (2002)