HIGHLIGHTS

ANGIOGENESIS

Herding vascular precursors

Angiogenesis is required for normal embryonic development, but also for tumour growth. Although a variety of growth factors have been identified that promote angiogenesis, little is known about the origin of the cells that contribute to tumour-associated vessels. In the November issue of *Nature Medicine*, David Lyden *et al.* report that bone-marrow-derived cells are recruited by vascular endothelial growth factor (VEGF) to the newly forming vasculature.

To identify the cells that contribute to tumour angiogenesis, the authors studied *Id*-mutant mice, which do not undergo postnatal angiogenesis. The Id proteins are transcriptional repressors that control differentiation. Although mice with reduced *Id* gene dosages ($Id1^{+/-}/Id3^{-/-}$) undergo normal development, they cannot support neo-angiogenesis or tumour growth.

Bone-marrow-derived endothelial-like cells have been shown to contribute to angiogenesis in ischaemic limbs, so the authors asked whether these cells could also contribute to tumour angiogenesis. They found that transplantation of wild-type bone marrow into $Id1^{+/-}/Id3^{-/-}$ mice restored tumour neo-angiogenesis and growth. Conversely, $Id1^{+/-}/Id3^{-/-}$ bone marrow engrafted into wild-type animals reduced tumour growth. This indicated that bone-marrow-derived cells could promote formation of new blood vessels.

But what specific cells in the bone marrow contribute to neo-angiogenesis? Lyden *et al.* tracked the transplanted cells with β-galactosidase. A few days after engraftment, a subpopulation of bone marrow cells, identified as circulating endothelial precursor cells (CEPs), incorporated into the lining of tumour blood vessels. These cells expressed one of the VEGF receptors, VEGFR2. Furthermore, myeloid precursors that expressed a different VEGF receptor, VEGFR1, contributed to formation of the blood vessel walls.

So, does VEGF signalling induce bone marrow cells to contribute to tumour angiogenesis? Increasing VEGF levels in the blood of wild-type mice induced co-mobilization of bone-marrow-derived $VEGFR2^+$ CEPs and $VEGFR1^+$ haematopoietic cells to the peripheral circulation. Administration of antibodies against VEGFR prevented mobilization and subsequent angiogenesis in wild-type mice.

Increasing the plasma concentration of VEGF also upregulated *Id1* and *Id3* expression in bone marrow cells of wild-type mice. Are Id1 and Id3 required for VEGF signalling? Apparently so, as in *Id*-mutant bone-marrow cultures, $VEGFR2^+$ CEPs and $VEGFR1^+$ myeloid precursors failed to expand after VEGF treatment. Furthermore, increasing plasma VEGF levels in *Id*-mutant mice failed to recruit bone-marrow-derived precursor cells to the peripheral circulation.

Tumour cells produce VEGF, and these findings indicate that one of the functions of this growth factor is to signal bone marrow $VEGFR^+$ progenitors, through Id1 and Id3, to move into the peripheral circulation and contribute to new blood vessels. Therapeutics designed to target these blood vessel precursors might be one way to slow tumour growth.

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References and links

ORIGINAL RESEARCH PAPER Lyden, D. *et al.* Impaired recruitment of VEGF-responsive bone marrow-derived precursor cells blocks tumor angiogenesis and growth. *Nature Med.* **7**, 242–248 (2001)

WEB SITES
Robert Benezra's lab:
http://www.ski.edu/lab_homepage.cfm?lab=137