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ANGIOGENESIS

Inside or outside?

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Inhibition of tumour angiogenesis using therapies directed against vascular endothelial growth factor (VEGF) has shown clinical efficacy against various tumour types. However, it is becoming clear that these inhibitors can induce toxicities by disrupting normal vascular homeostasis. Luisa Iruela-Arispe and colleagues have found that intracrine VEGF signalling in endothelial cells (ECs) is required for vascular homeostasis, but not for pathological angiogenesis, indicating that therapies that target VEGF from the outside of the cell (such as anti-VEGF antibodies) might have fewer toxicities than those that target it from the inside (such as VEGF receptor (VEGFR) tyrosine kinase inhibitors).

Iruela-Arispe and colleagues specifically deleted *Vegf* in the ECs of mice ($VEGF^{ECKO}$ mice) using Cre-Lox technology. Many $VEGF^{ECKO}$ mice (about 55%) died suddenly, owing to endothelial degeneration, probably as a result of EC apoptosis. Mice that survived into adulthood had systemic vascular pathologies, including haemorrhages and intestinal perforations. $VEGF^{ECKO}$ mice also had significant cardiac dysfunction, with reduced left ventricular ejection fraction and heart rate compared with wild-type controls. However, $VEGF^{ECKO}$ mice had a similar angiogenic response to control mice, as assessed using Matrigel plugs.

Interestingly, levels of VEGF in the plasma were not lower in $VEGF^{ECKO}$ mice, and reverse transcription PCR analysis showed no difference in *Vegf* expression levels in whole organs, indicating that circulating or tissue VEGF was unable to rescue the $VEGF^{ECKO}$ phenotype. Isolated ECs from $VEGF^{ECKO}$ mice did not survive well in culture following hypoxia-induced stress, and this was not rescued by exogenous VEGF, pointing to a role for autocrine VEGF signalling. Indeed, VEGFR2 was phosphorylated in cultured human ECs in hypoxic conditions in the absence of exogenous VEGF. This was blocked by the VEGFR2 tyrosine kinase inhibitor SU4312 (which acts intracellularly against VEGFR2) but not by the anti-VEGF antibody bevacizumab (which binds extracellular VEGF), indicating that the phosphorylation of VEGFR2 probably occurs intracellularly without VEGF secretion (intracrine signalling). Because $VEGF^{ECKO}$ mice have a normal angiogenic response, this intracrine signalling appears to not be required for angiogenesis.

These data have interesting implications for the use of anti-VEGF pathway therapies. Although studies in patients need to be conducted, it seems possible that the inhibition of extracellular VEGF could be less toxic but still inhibit tumour angiogenesis.

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ORIGINAL RESEARCH PAPER Lee, S. *et al.* Autocrine VEGF signalling is required for vascular homeostasis. *Cell* **130**, 691–703 (2007)
FURTHER READING Verheul, H. M. W. & Pinedo, H. M. Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. *Nature Rev. Cancer* **7**, 475–485 (2007)