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ANGIOGENESIS

Turning it down a Notch

The resistance of several tumour types to vascular endothelial growth factor (VEGF) inhibition has prompted the hunt for alternative molecular targets in the angiogenic cascade. A recent study confirms the NOTCH1 receptor as one such target.

Kitajewski and colleagues generated a soluble form of the NOTCH1 receptor (NOTCH1 decoy) that efficiently attenuated activation of NOTCH1 by its ligands jagged 1, delta-like 1 (DLL1) and DLL4, making it a pan-ligand inhibitor and a valuable tool with which to further study the role of NOTCH1 signalling in angiogenesis. The authors first examined the requirement for NOTCH1 in physiological angiogenesis and implanted a chamber containing $VEGF_{121}$-producing tumour cells under the dorsal skin of a mouse. Angiogenesis induced in the smooth muscle layer overlying the chamber was significantly reduced by coexpression of NOTCH1 decoy, suggesting that dermal angiogenesis requires NOTCH1 receptor activation.

The authors also observed that murine mammary tumour cells producing fibroblast growth factor 4 showed increased expression of jagged 1 and, based on this, they predicted that tumours arising from these cells would require NOTCH1 for growth and angiogenesis. Indeed, NOTCH1 decoy expression in these cells led to a significant reduction in tumour volume following subcutaneous implantation in mice. Furthermore, immunostaining and real-time PCR experiments confirmed a substantial decrease in both NOTCH1 signalling and tumour angiogenesis in NOTCH1 decoy-expressing tumours.

Next, the authors used human NGP neuroblastoma cells, which, as xenografts, develop a mature vasculature. Expression of the NOTCH1 decoy by NGP cells resulted in a marked reduction in xenograft viability and angiogenesis, accompanied by an increase in tumour cell apoptosis and intratumoural haemorrhage. NOTCH1 decoy expression also correlated with a loss of vessel continuity, suggesting that NOTCH1 signalling between neighbouring vascular cells is required to stabilize blood vessels in this system. Importantly, NGP cells are known to be refractory to VEGF blockade, so their vulnerability to NOTCH1 receptor inhibition suggests that this might be a promising alternative anti-angiogenic strategy for cancer.

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ORIGINAL RESEARCH PAPER Funahashi, Y. *et al.* A Notch1 ectodomain construct inhibits endothelial Notch signaling, tumour growth and angiogenesis. *Cancer Res.* **68**, 4727–4735 (2008)

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