ANGIOGENESIS

Hidden signatures written in blood

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URLs
CD276
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene&Cmd=ShowDetailView&TermToSearch=80381&ordinalpos=1&itool=EntrezSystem2.PEntrez.Gene.Gene_ResultsPanel.Gene_RVDocSum

Angiogenesis is a crucial feature of solid tumour biology, and anti-angiogenic therapies have become a major strategy for cancer treatment. However, current therapies disrupt both malignant (pathological) and normal (physiological) angiogenesis, resulting in side effects. Steven Seaman and colleagues have identified several genes that are selectively upregulated only in tumour blood vessels, and which could provide specific targets for tumour angiogenesis.

Seaman and colleagues first set out to unravel the comprehensive transcriptome of the normal mouse endothelium. They performed serial analysis of gene expression (SAGE) on purified endothelial cells from different murine tissues. By comparing these SAGE libraries they identified several organ-specific (for example, liver) endothelial transcripts that are upregulated 20-fold or more compared with all other normal endothelia from other organs. They next sought to identify genes that are upregulated by endothelial cells during normal physiological angiogenesis. They performed SAGE on endothelial cells isolated from murine liver at 24, 48 and 72 hours after a 70% partial hepatectomy — a period during which the liver regenerates and endothelial cells are thought to proliferate. Comparison of these transcriptomes with those of endothelial cells from normal non-proliferating organs identified 12 genes that are overexpressed in regenerating liver endothelial cells. Most of the 12 genes are involved in cell-cycle regulation, in keeping with the fact that these endothelial cells are dividing.

To identify genes that have increased expression during malignant angiogenesis but not in physiological angiogenesis, Seaman *et al.* performed SAGE on endothelial cells isolated from tumours and compared these transcriptomes to those of endothelial cells from normal resting tissue and from regenerating liver. They compared five tumours grown in mice: two grown in the liver from metastatic colon cancer cell lines of either mouse (CT26) or human (KM12SM) origin, and three grown subcutaneously from human colon cancer cells (SW620), mouse lung cancer cells (LLC) or mouse mammary cancer cells (EMT6). 13 genes were upregulated 10-fold or more in the endothelial cells from all five tumours, and were designated tumour endothelial markers (TEMs). 7 of the 13 TEMs encode cell surface receptors, of which the most differentially expressed was *CD276*.

But are these TEMs overexpressed in human cancers? *CD276* mRNA was undetectable by *in situ* hybridization in normal human colonic mucosa, but prominent in blood vessels from malignant colorectal tissues. Furthermore, CD276 expression was increased in colon and lung tumours, and staining with an anti-CD276 antibody revealed a vessel-like pattern in human colorectal, lung, breast, oesophageal and bladder cancers, but not in corresponding normal tissue. Importantly, CD276 was not detectable in the human corpus luteum (a useful control for physiological angiogenesis), indicating that CD276 is specifically overexpressed in the blood vessels of human tumours. Therefore, CD276 might be a useful target for tumour-specific anti-angiogenic therapies.

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ORIGINAL RESEARCH PAPER Seaman S. *et al.* Genes that distinguish physiological and pathological angiogenesis. *Cancer Cell* **11**, 539–554 (2007)
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