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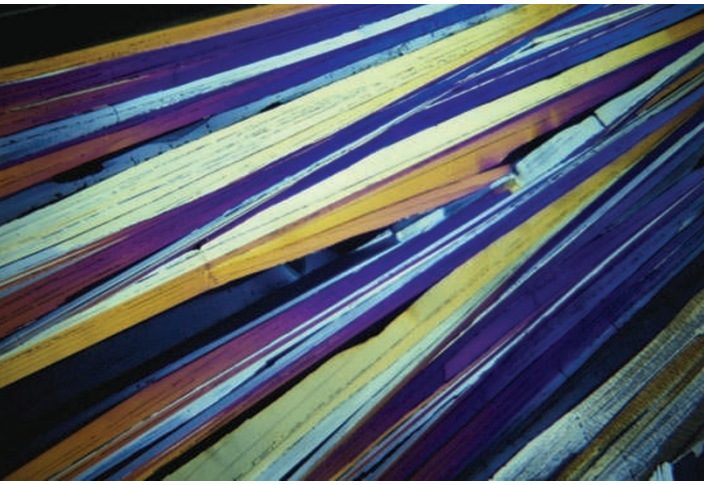
ANGIOGENESIS

Regulating vessel size

Angiogenesis is a crucial step in tumour progression and is therefore an attractive target for therapeutic intervention. However, dissecting the role of angiogenesis genes in disease *in vivo* can be challenging as knockouts of many of these genes are embryonic lethal. A unique approach that targets angiogenic genes in mouse embryonic stem (ES) cells therefore provides a valuable tool for understanding tumour angiogenesis.

Subcutaneous transplantation of ES cells into mice results in the formation of tumours that contain various cell types (teratomas). Gavin Thurston, George Yancopoulos and colleagues used a reporter-gene system to target vascular-specific genes in ES cells, allowing them to track the contribution to teratoma formation of ES cells that express these genes. They found that ES cells can give rise to endothelial cells, which form vascular networks, and that these cells comprise a substantial proportion (approximately 50%) of the total teratoma endothelial cells. The ES cell-derived endothelial cells had a similar gene expression profile to host-derived endothelial cells. The ES cell-derived vessel networks could also be perfused by a tracer, indicating that they were functional. Therefore, these results collectively suggested that ES cells can differentiate into bona fide endothelial cells in mouse teratomas.



Zhe Li *et al.* then used their ES cell teratoma system to investigate the role of individual vascular-specific genes in tumour angiogenesis by creating knockout ES cells. Specifically, they found that vascular endothelial receptor tyrosine phosphatase (*Veptp*)-knockout ES cells contributed to the teratoma vasculature and that *Veptp*-knockout blood vessels were larger in diameter and formed a less hierarchical pattern than host-derived blood vessels.

As the vessel phenotype in the *Veptp*-knockout tumours was reminiscent of previous findings when the angiopoietin (ANG)–TIE2 pathway was activated, the authors investigated the role of this pathway in ES cell-derived teratomas. They systemically treated teratoma-bearing mice with recombinant ANG1, which increased vessel diameter in host-derived, ES cell-derived and *Veptp*-knockout ES cell-derived blood vessels. Moreover, treatment of teratoma-bearing mice with a protein that blocks the interaction of ANG with TIE2 led to a dramatic reduction in ES cell-derived vessel size.

Is activation of the ANG–TIE2 pathway important for controlling blood vessel size in *Veptp*-knockout vessels? The authors found that TIE2 phosphorylation was significantly increased in *Veptp*-null tumours compared with control tumours, and that phosphorylation was further increased by systemic ANG1 treatment. Treatment with an ANG inhibitor decreased phosphorylation in the *Veptp*-null tumours to control levels. Therefore, these results indicate that VEPTP negatively regulates the ANG–TIE2 pathway by dephosphorylating TIE2.

The results of this study might have therapeutic potential, as targeting the ANG–TIE2 pathway may restrict tumour perfusion. In addition, as the ES cell-derived teratomas are composed of many different cell types, such as epithelial and muscle cells, the contribution of other essential signalling pathways to cell differentiation and function could also be studied using this model.

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ORIGINAL RESEARCH PAPER Li, Z. *et al.* Gene-targeted teratoma model reveals role of Tie2 and vascular endothelial receptor tyrosine phosphatase in regulating tumor angiogenesis. *Proc. Natl Acad. Sci. USA* 15 Dec 2009 (doi:10.1073/pnas.0911189106)