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Developing strategies for therapeutic angiogenesis: vascular endothelial growth factor alone may not be the answer

Sir,

There has been huge development in the understanding of the molecular processes involved in angiogenesis, and identification of many of the growth factors involved in this process. This has inevitably led to attempts to use these factors clinically to manipulate angiogenesis therapeutically. A wide range of clinical applications can be envisaged for increasing blood supply therapeutically in plastic and reconstructive surgery. These include reconstructive applications, such as prefabricating flaps or augmenting blood supply in failing flaps. There are also applications in wound healing. The majority of trials have concentrated on the ligand vascular endothelial growth factor (VEGF). However, VEGF alone may not be enough to encourage the formation of stable patent vessels in the treated tissue.¹

Angiogenesis can broadly be divided into a stage of initiation and a subsequent stage of vessel stabilisation. Initiation involves a co-ordinated cascade of endothelial-cell activation, migration, proliferation and differentiation to give rise to a new vessel. VEGF is a vascular-specific ligand that is a prime activator of angiogenesis, but there are other important growth factors, such as platelet derived growth factor (PDGF) and fibroblast growth factor, that act on both endothelial cells and non-endothelial cells in the formation of a stable vessel.² Blood vessels induced by VEGF alone are primarily leaky and non-patent,³ as well as being prone to regression on withdrawal of VEGF.⁴ However, the acquisition of periendothelial support cells can stabilise the newly formed vessels. Stabilisation and maturation of newly formed vessels requires further angiogenic factors, such as PDGF- β and angiopoietin-1.² In order to achieve a meaningful increase in blood supply, newly formed capillaries have to remodel themselves into functional vessels.

Angiopoietin is a vascular-specific ligand that acts upon the Tie-2 receptor. This receptor is essential for the formation of new blood vessels as it is involved in the integrity and stability of newly formed vessels.⁵ An increased understanding of pericyte-endothelial-cell interaction and identification of defects in Tie-2 have helped to identify some venous malformations,⁶ highlighting the broad potential benefits of increased understanding of the molecular processes of angiogenesis. Angiopoietin-1 can also decrease leakage from vessels,⁷ and acts by increasing adhesion between endothelial cells and periendothelial cells, involving activation of the Tie-2 receptor.

When angiopoietin-1 is coadministered with VEGF in a corneal model of angiogenesis, there is a significant increase in neovessel density and the number of patent vessels, compared with administration of VEGF alone.⁸ Coadministration of angiopoietin-1 and VEGF in an animal model of hind-limb ischaemia results in increased collateral formation compared with administration of VEGF alone.⁹ When angiopoietin-1 and VEGF are administered in viral vectors to cremaster muscle flaps in rats there is a significant increase in functional capillary density, with increased formation of mature vessels. There is an increase in capillary perfusion, with an increase in the number of mature and stable vessels.¹⁰

Whilst the studies using single agents will undoubtedly be milestones in the development of therapeutic strategies to increase flap survival, it seems likely that the optimal strategy for inducing angiogenesis therapeutically might involve using

an initial agent aimed at inducing vessel growth and a subsequent agent to promote stability and function.

Yours faithfully,

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References

1. Brindle NP, McCarthy MJ, Bell PR. Angiogenic revascularisation in ischaemic disease: molecular techniques hold promise, though they are still some way off. *BMJ* 1999;318:1500–1.
2. Risau W. Mechanisms of angiogenesis. *Nature* 1997;386:671–4.
3. Benjamin LE, Keshet E. Conditional switching of vascular endothelial growth factor (VEGF) expression in tumors: induction of endothelial cell shedding and regression of hemangioblastoma-like vessels by VEGF withdrawal. *Proc Natl Acad Sci USA* 1997;94:8761–6.
4. Benjamin LE, Hemo I, Keshet E. A plasticity window for blood vessel remodelling is defined by pericyte coverage of the pre-formed endothelial network and is regulated by PDGF-B and VEGF. *Development* 1998;125:1591–8.
5. Suri C, Jones PF, Patan S, et al. Requisite role of angiopoietin-1, a ligand for the TIE2 receptor, during embryonic angiogenesis. *Cell* 1996;87:1171–80.
6. Vikkula M, Boon LM, Carraway III KL, et al. Vascular dysmorphogenesis caused by an activating mutation in the receptor tyrosine kinase TIE2. *Cell* 1996;87:1181–90.
7. Thurston G, Suri C, Smith K, et al. Leakage-resistant blood vessels in mice transgenically overexpressing angiopoietin-1. *Science* 1999;286:2511–4.
8. Asahara T, Chen D, Takahashi T, et al. Tie2 receptor ligands, angiopoietin-1 and angiopoietin-2, modulate VEGF-induced post-natal neovascularization. *Circ Res* 1998;83:233–40.
9. Chae JK, Kim I, Lim ST, et al. Coadministration of angiopoietin-1 and vascular endothelial growth factor enhances collateral vascularization. *Arterioscler Thromb Vasc Biol* 2000;20:2573–8.
10. Lubiatowski P, Guranluoglu R, Goldman CK, et al. Gene therapy by adenovirus-mediated vascular endothelial growth factor and angiopoietin-1 promotes perfusion of muscle flaps. *Plast Reconstr Surg* 2002;110:149–59.

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A technique for preparing meshed skin grafts with planned expansion ratios

Sir,

A machine-meshed split-skin graft is an effective method of grafting large difficult wounds and burns.^{1,2} Sometimes the skin-meshing machine is unavailable. I offer a technique for producing a meshed skin graft with a predetermined expansion ratio. Established calculations are used to discuss how the measurements can be changed to produce various expansion ratios and how the measurements affect healing time. This hand meshing is easy and effective.

The split-skin graft is placed on a wooden skin-graft board, stretched and its corners fixed with staples to an underlying sterile theatre sheet. Rows and columns of uniform cuts in a set pattern are made with a no. 15 surgical blade. The geometric mesh pattern has the following parameters: the cuts have a fixed length, L , and fixed vertical, g , and horizontal, d , separations. First, two rows of cuts are measured and made; the cuts have length L , are separated from each other by $2d$ and have a vertical separation of g (Fig. 1(A)). Next, two new