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Apology: The Publisher apologises for the omission of A.J.P. Clover's name and affiliation in the first published version of the following letter (British Journal of Plastic Surgery 2003;56:77)

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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