Journal of Plastic, Reconstructive & Aesthetic Surgery (2008) 61, 1425–1437

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

REVIEW

Angiogenesis and plastic surgery

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Received 8 February 2008; accepted 29 May 2008

KEYWORDS
Angiogenesis;
Plastic surgery;
Flap survival;
Tendon healing;
Fracture healing;
Ulcer healing

Summary Angiogenesis, the formation of new blood vessels from an existing vascular bed, is a normal physiological process which also underpins many – apparently unrelated – pathological states. It is an integral factor in determining the success or failure of many procedures in plastic and reconstructive surgery. As a result, the ability to control the process would be of great therapeutic benefit. To appreciate the potential benefits and limitations of recent advances in our understanding of angiogenesis, it is important to comprehend the basic physiology of blood vessel formation. This review aims to summarise current knowledge of the way in which angiogenesis is controlled and to look at how disordered vessel development results in pathology relevant to plastic surgery. Through this we hope to provide a comprehensive overview of the recent advances in angiogenesis as they relate to plastic surgery, particularly the promotion of flap survival, tendon healing, nerve regeneration, fracture healing and ulcer treatments.

Angiogenesis is a normal physiological process which also underpins many apparently unrelated pathological states. It is a major determinant of the success or failure of many procedures in plastic surgery. Our increasing knowledge of how angiogenesis works and how it is controlled is beginning to make it possible to intervene in the process to the advantage of our patients. At its core, the final common pathways leading to angiogenesis are the same regardless of the initial stimulus – whether normal, pathological or deliberate. However, to fully appreciate these pathways it is helpful to have an understanding of normal vessel development beginning with the embryo. This review will then summarise current knowledge of the way in which angiogenesis is controlled and look at how disordered vessel development results in pathology relevant to plastic surgery. We will try to draw together the many different

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doi:10.1016/j.bjps.2008.05.041

strands of the story of angiogenesis as it relates to plastic surgery to provide an overview of what is already known and where current research is leading.

Formation of new blood vessels: what, why and where?

Two basic processes underlie the formation of blood vessels. These are vasculogenesis and angiogenesis. Vasculogenesis generally refers to the formation of the primitive vasculature in the embryo. Angiogenesis describes the extension of existing vessels into new areas (Figure 1).

Many key lessons in the field of blood vessel assembly have been learned from studies of embryo development. In the embryo, formation of the vascular system occurs via a combination of vasculogenesis and angiogenesis.[1,2] Extra-embryonic vasculogenesis involves the *de novo* differentiation of progenitor cells from mesoderm-derived precursor cells termed haemangioblasts.[3] Endothelial and haematopoietic cells are known to be derived from the same precursor cells because of the presence of common markers, including VEGF receptor type 2 (VEGF-R2), angiopoietin (Ang) receptors, VE-cadherin, CD31 and CD34.[4,5] The differentiated haemangioblasts form clusters of endothelial cells (or blood islands), which multiply and fuse to give rise to the dorsal aorta, cardinal vein and yolk sac. Intra-embryonic vascular development follows yolk sac vascularisation. The blood vessels differentiating inside the embryo are connected to the yolk sac by vitelline arteries and veins, which develop within the embryo. The primary capillaries are established by vacuolisation (intracellular lumen formation) or by intercellular lumen formation, by joining distal endothelial cells to a pre-existing lumen.[6] Mural cells develop from the epicardium, neural crest and mesenchyme but also from endothelial cells in the dorsal aorta, which can transdifferentiate into smooth muscle cells (Table 1).

After the development of the primary vascular system, the mature vasculature forms by remodelling of pre-existing vessels as a result of angiogenesis.[7] This involves a succession of events controlled by receptors and signalling molecules many of which are also important in vasculogenesis. Endothelial cells normally form a tight barrier between the flowing blood and underlying tissue as a consequence of interactions between matrix proteins and adhesion molecules. Sprouting angiogenesis involves many steps, including retraction of pericytes from the abluminal surface of capillaries, protease secretion by endothelial cells to disrupt cell-matrix interactions, degradation of extracellular matrix surrounding the pre-existing vessels and endothelial migration and proliferation towards the angiogenic stimulus. A provisional matrix is laid down, consisting of molecules such as fibrin and fibronectin. Cell adhesion molecules such as $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins mediate the interaction of the endothelial cells in the

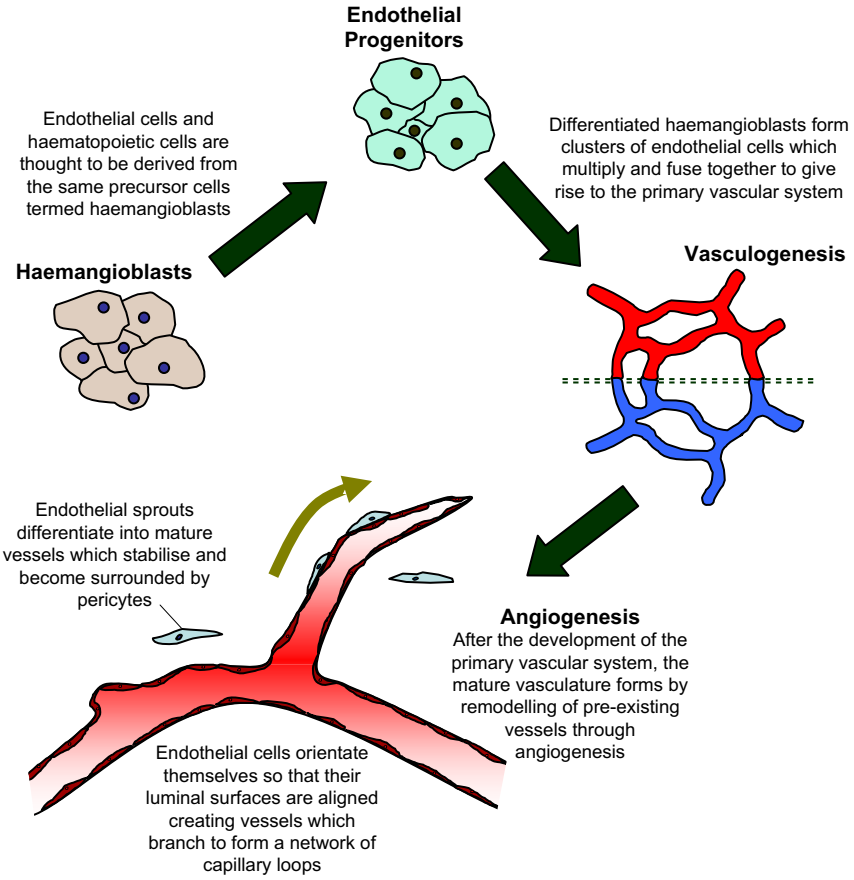

Figure 1 Formation of a vascular network.