



UNIVERSITY OF LEEDS

This is a repository copy of *Angiogenesis: growth points*..

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/88458/>

Version: Accepted Version

Article:

Egginton, S and Birot, O (2014) Angiogenesis: growth points. *Microcirculation*, 21 (4). 276 - 277. ISSN 1073-9688

<https://doi.org/10.1111/micc.12131>

Reuse

Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

UMIC-2014-0022

Angiogenesis: growth points

Stuart Egginton (University of Leeds, UK), Olivier Birot (York University, Canada)

Abstract

This collection of papers is based on talks presented at the IUPS meeting in Birmingham, UK last summer, in a symposium as part of the ESM & EVBO programme, sponsored by the British Microcirculation Society and *Microcirculation*. In this issue we discuss new insights into the control of angiogenesis, including regulation of different aspects of endothelial cell biology by the tissue stroma, during inflammatory disease, and active remodelling of the microcirculation. We address a variety of signalling modes that determine the endothelial responses to pro-angiogenic stimuli, including necessary synergy among different pathways and processes. We present an update of recent developments, and identify some areas where significant progress will likely occur.

Angiogenesis is the formation of new capillaries from pre-existing ones. These microvessels are key players in body homeostasis not only because they ensure an optimal match between oxygen/nutrient delivery and tissue metabolic demand, but also because of other key physiological functions they facilitate, such as hormonal signalling or immune surveillance. What is truly remarkable about the microcirculation is its plasticity in response to various physio-pathological stimuli. For example, capillaries grow as a result of muscle endurance training, during the menstruation cycle and wound healing, but inappropriately with psoriasis or diabetic retinopathy; their regression may be unwanted in peripheral vascular disease and post-myocardial infarction, but desirable during tumor growth.

For a few decades the concept of manipulating angiogenesis was of necessity rather simplistic: inhibiting the process in diseases presenting excessive angiogenesis, and stimulating it in the context of capillary rarefaction or impaired growth. Since Judah Folkman's pioneer work on tumor vasculature the 70's, numerous studies have focused on developing strategies to inhibit angiogenesis by targeting individual pathways, often involving vascular endothelial growth factor (VEGF). Unfortunately, while promising *in vitro* and in animal models, most of these therapeutic approaches have shown poor efficiency when translated into clinical trials attempting to starve cancer into submission. Some major issues are that inhibiting tumor vascularisation might favor hypoxic cell clusters, limiting delivery of chemotherapeutic drugs to the tumor cell mass, and adoption of alternative signalling pathways during treatment. The complexity of manipulating angiogenesis is also evident in treatment of peripheral vascular disease, where arterial obstruction leads to skeletal muscle ischaemia and compensatory angiogenesis is crucial to limit disease severity. Many studies have therefore attempted to pharmacologically stimulate expression of pro-angiogenic factors such as VEGF, but so far with limited success. Conversely, exercise training rehabilitation may be a simple, cost-effective intervention to limit tumour progression and promote angiogenesis in ischaemic muscle. Although it might not be suitable for all patients, it emphasises an important point: manipulating one or two

molecular targets is often not as powerful as stimulating coordinated angiogenesis using a physiological stimulus.

Such observations have forced us to reconsider the approach of therapeutic angiogenesis, requiring a better understanding of how capillary growth occurs from the perspective of a truly integrated process. Evidence for new directions are the reviews presented in this STI, based on a symposium sponsored by the journal at the IUPS in Birmingham last summer, and papers covering a range of stimuli, cellular cast and molecular players in the complex process that defines angiogenesis in health and disease.

The first paper by Hoying *et al.* [1] uses network architecture to demonstrate how angiogenesis involves reciprocal interaction between endothelium, interstitial matrix and stromal cells in order to direct new vascular growth. Mechanical forces derived from active tissue deformation may act as guidance cues, such that stromal influences may define the mature topology of the microcirculation. The next two papers examine the role mechanical factors may play in regulating *in vivo* angiogenesis. Wragg *et al.* [2] contrast the dominance of chemical signalling in pathological angiogenesis (endothelial chemotransduction) with the possibility of mechanotransduction as a major regulator due to shear stress dependent endothelial cell gene expression. Intriguingly, both high and low shear stress conditions are shown to be permissive for capillary growth, and there is a growing body of evidence suggesting that a combination of metabolic and mechanical signalling is needed for the observed tight feedback regulation. Hoier & Hellsten [3] report on the importance of skeletal muscle angiogenesis as an adaptation to exercise training that provides adequate diffusion capacity for oxygen and nutrients. Mechanical forces present during muscle activity are linked with enhanced expression of angiogenic factors. Focusing on the dominant growth factor (VEGF) they demonstrate how its interstitial secretion, acting on endothelial VEGF receptors, may initiate capillary growth. Ruhrberg *et al.* [4] take up the story of one receptor for which VEGF is a ligand, neuropilin 1, as a regulator of vasculogenesis, vessel remodelling and arteriogenesis. Positive roles, such as relieving tissue ischaemia, is contrasted with the detrimental aspects, e.g. promoting tumour growth with angiogenesis, and enhancing tissue oedema. Our current understanding about the roles played by its multiple ligands and signalling partners in vascular homeostasis is reviewed. Steagall *et al.* [5] consider another avenue whereby bioavailability of angiogenic regulators may be controlled. Extracellular ubiquitin is an immune modulator that increases levels of VEGF and MMPs in cardiac microvascular endothelial cells. This study demonstrated one mechanism by which this protein may facilitate myocardial angiogenesis, with potentially important consequences for tackling some cardiovascular diseases. Blood vessel growth clearly requires fine-tuned changes in cell shape, and intermediate filaments play an important role in regulating the cytoskeleton. Dave & Bayless [6] describe how novel functions of vimentin in cell adhesion and migration, regulated in complex post-translational modifications, are required for endothelial cell invasion of the extracellular matrix that is an essential part of the angiogenesis cascade. Kelly-Gros *et al.* [7] consider the role of perivascular pericytes as a potential target for angioregulatory therapies. Although interest in these cells go back over a century, our understanding is limited by inadequate readouts of pericyte identity and lineage. This review identifies many unanswered questions that require addressing before their therapeutic potential may be realised. Finally, Ashraf [8] discusses how angiogenesis may contribute to many features of osteoarthritis including inflammation, joint damage and pain. It is known that angiogenic

modulators may be common to both vessel and nerve growth, and this review examines how one complex protein kinase may be involved in modulating angiogenesis mediated pathology.

References

- 1] Hoying J, Weiss J, Utzinger Urs. (2014). Formation of microvascular networks: role of stromal interactions directing angiogenic growth. UMIC-2013-0114.R1
- 2] Wragg JW, Durant S, McGettrick HM, Sample KM, Egginton S, Bicknell R. (2014). Shear stress regulated gene expression and angiogenesis in vascular endothelium. UMIC-2013-0124
- 3] Hoier B, Hellsten Y. (2014). Exercise induced capillary growth in human skeletal muscle and the dynamics of VEGF. UMIC-2013-0117
- 4] Plein A, Fantin A, Ruhrberg C. (2014). Neuropilin regulation of angiogenesis, arteriogenesis and vascular permeability. UMIC-2013-0102
- 5] Steagall R, Daniels C, Dalal S, Joyner W, Singh M, Singh K. (2014). Extracellular ubiquitin increases expression of angiogenic molecules and stimulates angiogenesis in cardiac microvascular endothelial cells. UMIC-2013-0082
- 6] Dave J, Bayless K. (2014). Vimentin as an integral regulator of cell adhesion and endothelial sprouting. UMIC-2013-0101
- 7] Kelly-Goss M, Sweat R, Stapor P, Peirce S, Murfee W. (2014) Targeting pericytes for angiogenic therapies. UMIC-2013-0103
- 8] Ashraf S. (2014). Angiogenesis: a therapeutic target in osteoarthritis, potential role for calcium/calmodulin-dependent protein kinase II. UMIC-2013-0108