The development of blood vessels is essential for organ growth in the embryo and repair of wounded tissue in the adult. However, an imbalance in this process contributes to the pathogenesis of a number of disorders including cancer that is now recognized as the result of not only uncontrolled malignant cell proliferation but also uncontrolled vessel growth. The existence of tumour-derived factors responsible for promoting new vessel growth was postulated over 70 years ago, and a few years later, it was proposed that tumour growth is crucially dependent on neo-vascular supply. In 1971, pioneering work by Judah Folkman, who sadly passed away on 14 January 2008, suggested that inhibition of angiogenesis would be an effective strategy to treat human cancer, leading to the development of an active search for angiogenesis inducers and inhibitors. In less than 15 years, an explosion of interest in angiogenesis research has generated the necessary insights to develop the first clinically approved anti-angiogenic agents.1 Several additional common disorders such as psoriasis, arthritis, blindness, obesity, asthma, atherosclerosis, and infectious disease are associated with excessive angiogenesis.2

Alternatively, insufficient vessel growth and abnormal vessel regression can lead to ischaemic diseases as well as to neuro-degeneration, hypertension, pre-eclampsia, respiratory distress, osteoporosis, and other disorders. Over the past decade, intensive efforts have also been undertaken to develop therapeutic strategies to promote revascularization of ischaemic tissues. Unfortunately, clinical trials testing the pro-angiogenic potential of vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) failed to demonstrate any beneficial effects. Novel strategies, involving transplantation of progenitor vascular cells or the delivery of agents capable of stimulating the growth not only of distal capillaries but also of pre-existing collaterals, are now being tested in experimental models as well as in the clinical arena.3

Overall, angiogenesis research will probably change the face of regenerative medicine in the next decades, with many patients worldwide predicted to benefit from pro- or anti-angiogenesis treatments. This special spotlight issue of Cardiovascular Research was designed to highlight recent advances in the understanding of molecular, genetic, and cellular mechanisms of vessel growth and their possible implications for regenerative medicine.

Vessel formation and growth is a highly orchestrated process involving numerous growth factors, chemokines, proteases, and inflammatory cells that play different roles in promoting and refining this process. In particular, because sprouting angiogenesis is an invasive process, proteolytic activities are required. Several members of the matrix metalloproteinases, MMP-2, MMP-9 and MT1-MMP and the related ADAMs (a disintegrin and metalloproteinase domain), are needed for activation and modification of growth factors and chemokines, ectodomain shedding with accompanied receptor activation and generation of protein fragments with pro- or anti-angiogenic activities. Proteases also facilitate the mobilization of vascular progenitor cells from the bone marrow and homing of these cells into the angiogenic area, as reviewed here by Van Hinsbergh and Koolwijk.4 Proteolysis leads to removal of obstructing matrix proteins and generation of space for endothelial cell migration. Endothelial cells that line blood vessel walls dynamically modify their integrin-mediated adhesive contacts with the surrounding extracellular matrix, leading to endothelial cell migration. Opposite autocrine and paracrine loops of factors regulate integrin function. As described by Serini et al.,5 semaphorin signalling through plexin has been shown to regulate endothelial integrin function and angiogenic remodelling.

Migration and proliferation of endothelial cells are also controlled by numerous growth factors and signalling pathways, as illustrated by several original articles in the issue. Thus, haeme oxygenase, which catalyses the rate-limiting step in the degradation of haeme to ferrous iron, mediates VEGF-A-induced endothelial cell proliferation. Accordingly, pharmacological inhibition of haeme oxygenase reduces blood flow recovery, capillary density, and progenitor cell mobilization in mice with hindlimb ischaemia.6 The lysophospholipid mediator sphingosine-1-phosphate (S1P) acts on vascular endothelial cells to stimulate migration and proliferation. Local exogenous S1P administration, or endogenous S1P overproduction using sphingosine kinase 1 transgenic mice, promotes post-ischaemic neovascularization.7 S1P is

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also involved in the effect of pro-angiogenic agents such as epoxygenosatrienolic acids (EETs). Indeed, knock-down of sphingosine kinase 1 by specific siRNA inhibits EET-induced endothelial cell proliferation and migration.8

The effect of pro-angiogenic factors may depend on the microenvironment as well as on the existence of non-canonical signalling. Along these lines, an original contribution within this issue demonstrates that the angiogenic effect of VEGF-C is markedly attenuated in the presence of a growing lymphatic network.9 Several FGFs and their tyrosine kinase receptors play a key role in angiogenesis. However, recent evidence strongly implicates non-tyrosine kinase receptors (NTKR), such as syndecan-4, αvβ3 integrin, or cell-surface FGF receptor-interacting proteins, as important players in FGF signalling. The relevance of non-canonical FGF signalling in angiogenesis is reviewed by Murakami et al.10

Physical forces generated within the vascular network are also major triggers of vessel growth. In particular, blood flow controls vascular patterning and maintenance of arterial-venous identity and drives the guidance of lumened vessel sprouts during embryogenesis. The impact of mechanical factors in vascular development is discussed in this issue by Le Noble et al.11 In an original study addressing the effect of mechanical forces on the orientation of angiogenic microvessels, Krishnan et al.12 report that neovessels align parallel to the direction of the stretch and that this may be due to collagen fibril alignment induced by the growing vessels themselves. In adult networks, physical factors play an essential role in adaptation to arterial occlusion in the context of peripheral and cardiac ischaemia. Endothelial cells respond to elevation of fluid shear stress by an increased production of endothelial adhesion molecules, chemokines, and chemokine receptors. Chemokines are chemoattractive proteins that regulate accumulation of leukocytes at inflammatory sites. The most extensively studied chemoattractant contributing to post-ischaemic neovascularization is monocyte chemoattractant protein-1 (MCP-1). Upregulation of chemoattractant molecules triggers infiltration of different types of inflammatory cells in the ischaemic area. The levels of monocytes and T lymphocytes directly correlate with the intensity of neovascularization. In this spotlight issue, we review the role of inflammation in vessel growth.13 Balestrieri et al.14 discuss in depth agents that are able to inhibit angiogenic activities or promote angiostatic activities of CXC chemokines. Alternatively, chemokines may act as direct pro-angiogenic agents. In one of the original contributions within this issue, Ryu et al.15 demonstrate that activation of fractalkine and its cognate receptor CX3CR1 upregulates HIF-1α and subsequently VEGF-A, leading to post-ischaemic neovascularization. Finally, inflammation also facilitates remodelling, likely through upregulation of MMP expression, as revealed by Bakker et al.16 in this issue.

Emerging evidence indicates that age and other risk factors for cardiovascular diseases, such as hypercholesterolemia, diabetes, smoking, and hypertension, impair the intrinsic capacity for vessel growth. Three reviews analyse the impact of cardiovascular risk factors such as diabetes and hypertension on the multiple steps involved in blood vessel growth and remodelling, including progenitor cell mobilization, efficacy of multiple angiogenic effector cells, and responsiveness of the vascular network.17–19

Finally, one of the most challenging discoveries in the field of angiogenesis is the recent demonstration that modulation of angiogenesis may affect obesity, as reviewed in detail by Lijnen.20 In addition, original contributions explore the role of two different adipokines, visfatin and adiponectin, on the angiogenic phenotype, suggesting that there is a real option to evaluate the efficiency of anti-angiogenic agents in obesity models in vivo.

In conclusion, the reviews and original articles collected in this spotlight issue devoted to cellular and molecular mechanisms governing blood vessel growth may help to pave the way for establishing more effective pro- and antiangiogenic therapies.

References