Arteriogenesis Versus Angiogenesis: Two Mechanisms of Vessel Growth

I. Buschmann and W. Schaper

After birth, new blood vessel formation proceeds via angiogenesis or arteriogenesis. Angiogenesis (capillary sprouting) results in higher capillary density. Arteriogenesis (rapid proliferation of collateral arteries) is potentially able to significantly alter the outcome of coronary and peripheral artery disease. The processes share some growth features but differ in many aspects.

The formation of a functional, integrated vascular network is a fundamental process in the growth and maintenance of tissue. Vascularization occurs by three distinct processes: vasculogenesis, angiogenesis, and arteriogenesis.

Vasculogenesis is the earliest morphogenetic process of vascular development and takes place exclusively during the early embryonic stages. Indeed, the cardiovascular system is the first organ system that is laid down during embryonic development. Vasculogenesis consists of the differentiation of angioblasts (the precursors of endothelial cells) into blood islands, which then fuse to form primitive capillary plexuses (2). The plexuses subsequently grow by angiogenesis (sprouting and tube formation by single endothelial cells within a preexisting capillary plexus), invade target tissues, and give rise to the primitive vascular system of embryonic organs. When the heart starts beating (after 2 days in the chick embryo) and the circulation commences shortly thereafter, significant changes occur in the morphogenesis of the vascular system. Some vessels of the primary plexus remain as capillaries, whereas others differentiate into arteries or veins (10). Although regression and differentiation are still unknown processes, it is believed that hemodynamic forces play a central role. Cessation of blood flow into a capillary segment causes the regression of the vessel, whereas an increase in pressure and shear stress may be an inductive factor for the local recruitment of smooth muscle cells, leading to the differentiation of a capillary vessel into an artery or vein. The adult vasculature, with a surface area of ~1,000 m², finally consists of large arteries, internally lined by endothelial cells and well ensheathed by smooth muscle cells, that progressively branch into smaller and smaller vessels, terminating in precapillary arterioles that then give rise to capillaries. These vascular tubes are comprised almost entirely of endothelial cells that are only in a few cases coated by a smooth muscle cell like the pericyte. The capillaries then feed into postcapillary venules that progressively associate into larger and larger venous structures (15).

The term angiogenesis was introduced in 1935 by Hertig to describe the formation of new blood vessels in the placenta and, later, in 1971, by Folkman to describe the neovascularization accompanying the growth of solid tumors. Angiogenesis is a process by which new capillary blood vessels sprout from a preexisting blood vessel.

I. Buschmann and W. Schaper are in the Department for Experimental Cardiology of the Max Planck Institute for Physiological and Clinical Research, Benekestrasse 2, D-61231 Bad Nauheim, Germany.

“Vasculogenesis consists of the differentiation of angioblasts….”
channels. The first step in the activation of the endothelium is the opening of chloride channels...

Activation of the endothelium

It is presently not well enough known how the stimulus of increased shear stress is transmitted from the endothelial cell membrane to the nucleus, where it initiates the transcriptional activity of a number of genes (12), partially via a protein that binds to the shear stress responsive element that is present in the promotor of several genes (NOS, PDGF, MCP-1). The first step in the activation of the endothelium is the opening of chloride channels that are also responsible for the volume control of endothelial cells. Characteristically stress-activated endothelium appears swollen in scanning electron microscopic images (15). Adhesion molecules are upregulated (4), and the conditions are perfect for the adhesion and invasion of circulating cells.

Circulating cells invade arterioles with activated endothelium

The upregulated expression of monocyte chemoattractant protein-1 (MCP-1) by endothelium attracts monocytes that adhere to and invade arteriolar collaterals. They in turn become activated (9), produce tumor necrosis factor-α and attract more monocytes. Platelets also adhere and produce interleukin-4, which increases the expression of more adhesion molecules. Upregulation of survival factors for monocytes (granulocyte macrophage colony-stimulating factor) provides the environment for a stable function of monocytes (Fig. 1C). These in turn produce fairly large amounts of growth factors, in particular, fibroblast growth factor-2. The adhesion and invasion of monocytes and platelets (also potent producers of growth factors) is soon followed by the first wave of mitosis of the endothelial and smooth muscle cells. Other cir-
Culminating cells that are implicated in vascular growth are the basophils, which transform into mast cells after they have entered the tissue compartment, where they produce heparin and autacoids that share in the process of arteriogenesis. The cell invasion is most prominent in the intima, the initial entrance, but even more pronounced later in the adventitia, where they create an inflammatory environment that is later accompanied by T cells. One of the effects of the perivascular inflammation is that it creates the space (by forcing neighboring tissue cells into apoptosis) for the greatly expanding collateral vessel, which can increase its diameter up to 20 times.

FIGURE 1. A: angiography of the rabbit hindlimb (7-day phosphate-buffered saline infusion) after femoral artery occlusion. B: angiography of the rabbit hindlimb [7-day monocyte chemoattractant protein-1 (MCP-1) infusion] after femoral artery occlusion. The number as well as the density of the collateral vessels increased significantly. Collateral arteries show a typical corkscrew pattern. C: histological section (midzone of the proliferating collateral artery) after 7 days of MCP-1 infusion. Several macrophages can be observed around the vessel. Provided by Dr. Dimitri Scholz.
Recently, circulating cells presenting CD-34 antigens on their surface were reported for their angiogenic potential. This is an interesting addition to the already existing list of circulating cells with an involvement in vascular growth.

Remodeling

Mitosis alone is not enough to rebuild an artery from an arteriole. The old structure is in large part dismantled and replaced. Two phases of arteriogenesis can be observed, the proliferating and remodeling phases. Proliferation of the endothelium is followed by smooth muscle cell mitosis, disruption of the lamina elastica interna, migration of vascular smooth muscle cells to form a new neointima, tissue lysis, and cell death of the perivascular tissue to create the space for the growing and expanding new artery. The new smooth muscle is to a large extent intimal and exhibits a longitudinal and helical orientation. It consists of dedifferentiated smooth muscle that has lost most of its differentiation markers, including loss of most of the actin filaments. It represents the “synthesis” type of smooth muscle cells in contrast to the physiological “contractile” type. The synthesis type produces extracellular matrix, collagen, and elastin and will finally produce a new internal elastic lamina. After months (6–12 mo in the canine heart model) the new collateral artery is almost indistinguishable from a normal artery, except for a slightly higher collagen content between the smooth muscle layers. In particular, the prominent intima is no longer detectable (11).

Therapeutic arteriogenesis

In previous studies we showed that chronic intra-arterial infusion of MCP-1 greatly increased the development of arterial collateral blood vessels (arteriogenesis) after femoral artery occlusion (6, 7). These collaterals were more numerous on angiograms, and their ability to conduct blood had increased by sixfold (Fig. 1, A and B). The histological appearance of these typical corkscrew vessels was that of muscular arteries. In another study, we injected a single dose of lipopolysaccharide intravenously into New Zealand White rabbits 3 days after ligation of the femoral artery (1). This potent stimulator of tumor necrosis factor-α also markedly enhanced the number of monocyte-derived macrophages accumulated around growing collateral arteries. Peripheral and collateral conductances were markedly increased. Nevertheless, on a molar basis MCP-1 is the most potent arteriogenic peptide. Vascular endothelial growth factor (VEGF) is a peptide with angiogenic properties. It is produced by cells in close vicinity of endothelial cells, suggesting paracrine regulation of capillary formation; it is secreted and exerts a direct effect via interaction with endothelial receptors Flk-1 and Flt-1; its chemoattractive action on monocytes is dose dependent; and its expression is highly regulated by hypoxia and thereby a physiological feedback mechanism to tissue hypoxia (3).

No role for ischemia/hypoxia

In contrast to angiogenesis, which relies on hypoxia, arteriogenesis does not. Hypoxia is known to transcriptionally upregulate the expression of VEGF, but posttranscriptional mRNA stabilization may even be more important. VEGF is able to circumvent the hypoxia-induced translation inhibition, and we have observed in our rabbit model of hindlimb ischemia that VEGF expression and capillary growth are indeed restricted to ischemic regions. However, collateral artery growth (arteriogenesis) occurs in nonhypoxic tissue. Resting blood flow in the thigh muscles, where collaterals develop after femoral artery occlusion, is not decreased, its ATP and phosphocreatine content is normal, and hypoxia-induced gene transcription (LDH-A, VEGF) is not activated. The distance between ischemic regions and the predilection sites for collateral growth can indeed be absurdly large, up to 70 cm between a patient’s gangrenous big toe and collaterals spanning a femoral or popliteal occlusion. Despite that, collateral artery growth is not exclusively controlled by the availability of mitogenic peptides but also by the presence of its receptors; endothelial cells in vivo and under normal physiological conditions apparently do not present their receptors. Only certain experimental or pathological situations (expolantation, in vivo culture, embryonic development, cytokine application) induce the expression and presentation of receptors, the mechanism of which is largely unknown. Only the simultaneous presence of the growth factor and its receptor can orchestrate the initiation of arterial vessel growth.

Conclusion

Arteriogenesis is by far the most efficient adaptive mechanism for the survival of ischemic limbs or internal organs such as heart and brain because of its ability to conduct, after adaptive growth, relatively large blood volumes per unit of time. An increase in the number of capillaries, the result of stimulated angiogenesis, is unable to do that. Arteriogenesis differs from angiogenesis in several aspects, the most important being the
dependence of angiogenesis on hypoxia and the dependence of arteriogenesis on inflammation. However, angiogenesis and arteriogenesis share several mechanisms of action (Fig. 2), e.g., their dependence on growth factors. Whereas angiogenesis can be largely explained by the actions of VEGF, arteriogenesis is probably a multifactorial process in which several growth factors are orchestrated. The role of VEGF in arteriogenesis is not clear, but a chemoattractive role for monocytes and hence an indirect contribution is imaginable.

The authors thank Dr. Borja Fernandez, for suggestions in the embryology part of this review, and Dr. Dimitri Scholz and Prof. Jutta Schaper, who provided histological preparations. Owing to space constraints, many relevant primary references have been regretfully omitted.

References


FIGURE 2. Mechanisms of action of angiogenesis and arteriogenesis. VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor.

In Forthcoming Issue

Ca2+ Sparks in Cardiac Muscle: Is There Life Without Them?
Ernst Niggli

The ether-à-go-go-Related Gene K Current: Functions of a Strange Inward Rectifier
Jürgen R. Schwarz and Christiane K. Bauer

Probing Nanometer Structures With Atomic Force Microscopy
Zhifeng Shao