Angiogenesis and Arteriogenesis: Two Distinct Types of Vessel Growth

Angiogenesis is the sprouting of capillaries. It results in a new developing network of endothelial tubes that is not surrounded by mural cells is fragile and prone to rupture, any new developing network of endothelial tubes that is not surrounded by mural cells is fragile and prone to rupture, and depending on the pressure gradient between the interconnecting networks, there is only minimal net forward flow, but small amounts of flow may oscillate within the network. A sudden arterial occlusion or a slowly progressing stenosis, a steep pressure gradient along the shortest path within the interconnecting network develops that increases blood flow velocity and hence fluid shear stress in these vessels that now assume the new function as “collaterals.”

The effect of this sustained increase in shear is the upregulation of distinct processes in the collateral arteries: upregulation of adhesion molecules (eg, vascular cell and intercellular adhesion molecules), increased endothelial production of several cytokines (monocyte chemoattractant protein-1, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor-α), attraction of circulating monocytes along the chemotactic gradient to the activated endothelium, production of nitric oxide, adhesion and invasion of monocytes, and maturation to macrophages. These in turn create an inflammatory environment and produce fairly large amounts of growth factors, particularly fibroblast growth factor-2 (FGF-2).

The invasion of monocytes is soon followed by the first wave of mitosis of the endothelial and smooth muscle cells (proliferating phase). Besides mitosis, the perivascular inflammation creates the space for the greatly expanding collateral vessel that can increase its diameter up to 20 times. The old structure is, in large part, dismantled and replaced primarily by new intimal and medial smooth muscle cells (remodeling phase). Finally, arteriogenesis results in a functional “new” artery originating from a preexisting arteriole.

What Is the Physiological Basis of an Efficient Perfusion of Internal Organs or Hind-limbs?

After sudden or slowly progressing stenosis of a major artery, the survival of ischemic limbs or internal organs like heart and brain can be guaranteed only if relatively large blood volumes per unit of time are made available to perfuse the ischemic territories. Taking the law of Ohm into account, blood pressure, resistance, and blood flow are closely linked to each other. The bigger the diameter of a vessel, the lower the resistance and hence the higher the blood flow. Preexisting collateral anastomoses, for instance, have the ability to conduct, after adaptive growth, relatively large blood volumes per unit of time. In many cases, collateral arteries can minimize or even prevent the fatal consequences of sudden arterial obstruction. This protective role of collateral arteries depends largely on their ability to increase their vessel diameter in a very short period of time by active proliferation. In the rabbit hindlimb, for example, collateral arteries increase their lumen 20-fold after experimentally induced femoral artery ligation. This restoration of blood flow cannot be achieved by an increased number of capillaries, the result of stimulated angiogenesis. Depending on the diameter of a single collateral artery (rabbit hindlimb after 7 days of femoral occlusion; collateral artery, ∼200 to 300 μm), many hundred thousands of these capillaries (diameter, ∼4 to 6 μm) would be needed to replace 1

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collateral artery (despite significant energy losses inherent to blood flow in small vessels).

**What Are the Promoters of Angiogenesis or Arteriogenesis?**

There is increasing evidence that angiogenesis relies on hypoxia, whereas arteriogenesis does not. Hypoxia is known to transcriptionally upregulate the expression of vascular endothelial growth factor (VEGF), but posttranscriptional mRNA stabilization may be even more important. VEGF is able to circumvent the hypoxia-induced translation inhibition, and in a rabbit model of hindlimb ischemia, VEGF expression and capillary growth are indeed restricted to ischemic regions. However, collateral artery growth (arteriogenesis) occurs in nonhypoxic tissue.7 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 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 controlled not only 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 (explantation, in vivo culture, embryonic development, and 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.

However, if hypoxia is not primarily responsible for arteriogenesis, which factor induces the rapid proliferation of preexisting collateral anastomoses? The earliest concept that explained the growth of collateral arteries compensating for the consequences of an atherosclerotic occlusion was that of Thoma,18 who stated in 1893 that the velocity of blood flow the consequences of an atherosclerotic occlusion was that of explained the growth of collateral arteries compensating for preexisting collateral anastomoses? The earliest concept that

References


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