REVIEW

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Angiogenesis *versus* arteriogenesis

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Abstract

In the vascular system, angiogenesis and arteriogenesis play a unique yet equally important role in both health and disease. Angiogenesis, the formation of new blood vessels from a preexisting vascular bed, occurs naturally during wound healing, the female menstrual cycle and pregnancy. It plays a critical role in tissue growth and repair, and is a highly controlled process that is dependent on an intricate balance of both pro-angiogenic (to stimulate) and anti-angiogenic (to negatively regulate the phenomenon) factors. Otherwise, the term arteriogenesis refers to anatomic transformation of preexisting arterioles with increasing lumen area and wall thickness, due to a thick muscular layer and purchasing of visco-elastic and vasomotor capacities. Arteriogenesis differs from angiogenesis in several aspects, the most important being the dependence of angiogenesis on hypoxia and the dependence of arteriogenesis on inflammation. The expression of growth factors and the cooperation of surrounding and infiltrating cells seem to be essential in orchestrating the complex processes during arteriogenesis.

Keywords: angiogenesis, arteriogenesis, hypoxia, VEGF.

Angiogenesis

The cardiovascular system is the first functional organ system to develop in the vertebrate embryo. Several genetic and epigenetic (vascular branching, pruning, remodeling) mechanisms are involved in the early development of the vascular system. During embryonal life, blood vessels first appear as the result of vasculogenesis, *i.e.*, the formation of capillaries from endothelial cells differentiating *in situ* from groups of mesodermal cells. Vasculogenesis consists of the differentiation of angioblasts (the precursors of endothelial cells) into blood islands, which then fuse to form primitive capillary plexuses. The primitive heart and primitive vascular plexus are formed in this way [1].

Further observations have indicated that vasculogenesis may not be restricted to early embryogenesis, but may also have a physiological role or contribute to the pathology of vascular diseases in adults. The major evidence in favor of this new view comes from: (*i*) demonstration of the presence of circulating endothelial cells and endothelial precursor cells; (*ii*) newly described mechanisms of blood vessel formation in tumor growth [2].

With the onset of embryonic circulation, these primary vessels have to be remodeled into arteries and veins in order to develop a functional vascular loop. Remodeling of the primary vascular plexus into a more mature vascular system is thought to occur by a process termed angiogenesis.

Embryonic vessel formation is also highly dynamic and subject to intense pruning and remodeling throughout development, with vessel tracts appearing and disappearing and links between vessels severing and then reconnecting in entirely new patterns [3]. Local alterations in perfusion produce dramatic changes in vascular patterning throughout the embryo [4]. In adult vessels, vessel segments can adapt to the amount of flow carried [5, 6].

Angiogenesis, the formation of new blood vessels from a preexisting vascular bed, occurs naturally during wound healing, the female menstrual cycle and pregnancy. It plays a critical role in tissue growth and repair, and is a highly controlled process that is dependent on an intricate balance of both pro-angiogenic (to stimulate) and anti-angiogenic (to negatively regulate the phenomenon) factors. The complex and dynamic angiogenic process occurs in an ordered highly orchestrated series, involving interactions between growth factors, vascular components (such as endothelial cells, vascular pericytes, fibroblasts, smooth muscle cells) and the extracellular matrix. Angiogenesis is a complex phenomenon consisting of several distinct processes, which include endothelial migration and proliferation, extracellular proteolysis, endothelial differentiation (capillary tube formation), and vascular wall remodeling.

Angiogenesis is stimulated by numerous 'classic' factors and other 'non-classic' regulators. Classic stimulators mostly include growth factors and cytokines, among which vascular endothelial growth factor (VEGF), placental growth factor (PlGF), platelet-derived growth factor (PDGF), fibroblast growth factor-2 (FGF-2), transforming growth factors (TGFs), angiopoietins (Angs). Non-classic factors include numerous endogenous peptides, among which erythropoietin (Epo), granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukins, angiotensin II (Ang II), endothelins (ETs), adrenomedullin (AM), proadrenomedullin N-terminal 20 peptide (PAMP), urotensin-II (U-II), leptin, adiponectin, resistin, neuropeptide-Y, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP) and substance P [7].

Arteriogenesis

Functional studies on arteriogenesis began in 1785 with the Scottish anatomist Sir John Hunter (1728–1793),

who documented his findings on the occlusion of the external carotid artery of a buck, and its physiological consequences. He observed that the animal's ipsilateral antler became cool to touch and its arterial pulse became impalpable, as its blood supply was dependent on the ligated artery. However, when the animal was reexamined a week later, the temperature and arterial pulsations of the antler had normalized. On further examination, Hunter found that small branches of the artery above and below the ligature had enlarged, and through their anastomoses the blood supply was restored [8].

During embryonic life, differentiation of arteries and veins was thought to be governed by hemodynamic forces, molding these vessels from the primary vascular plexus. Thoma [9] observed that vessels carrying a lot of blood widen, whereas those that carry little flow regress. Murray [10] postulated that vessels adapt to flow in order to optimize the shear stress to which they are subjected. These studies have shown that flow can alter lumen dimensions of arterial segments. 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 increased flow leads to increased fluid shear stress, which is proportional to the velocity of blood flow. In turn, shear stress acts directly upon gene expression involved in the endothelial cell cycle.

Ligation of extraembryonic artery induces a morphological and genetic transformation of arteries into veins and *vice versa* [4]. Grafts of embryonic quail arteries and veins demonstrated that arterial cells can colonize veins of the host and *vice versa* [11]. More recently, Pardanaud *et al.* [12] have shown that sympathetic innervations promotes arterial endothelial cell fate *in vivo*. Removal of the sympathetic nerves decreased arterial fate and leads to colonization of veins.

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. Moreover, the arterial morphogenesis occurring during embryonic development includes remodeling of the primary embryonic plexus making artery trees [13].

In postnatal life, the term arteriogenesis refers to anatomic transformation of preexisting arterioles with increasing lumen area and wall thickness, due to a thick muscular layer and purchasing of viscoelastic and vasomotor capacities [14]. The growth of arterioles in skeletal muscle results from preexisting capillaries recruiting smooth muscle cells [15]. This term is used to indicate: (*i*) the extension of an arterial tree occurring during postnatal life [16]; (*ii*) the transformation of native microvascular collateral arterioles into functional arteries after ischemic injury with consequent recovery of blood flow [17–21].

Arteriogenesis differs from angiogenesis in several aspects, the most important being the dependence of angiogenesis on hypoxia and the dependence of arteriogenesis on inflammation. Arteriogenesis occurs in non-hypoxic tissue, and has often been used to denote the remodeling of native microvascular collateral arterioles into arteries. A collateral vessel, resulting from the arteriogenic process, always conducts arterial blood flow and cannot become hypoxic. Collateral vessels in the vascular periphery are surrounded by normoxic tissue, Deindl *et al.* [22] analyzing several time points after occlusion of the femoral artery neither could detect an increased expression level of hypoxia-inducible factor 1-alpha (HIF-1α) mRNA nor an up-regulation of the HIF-1-controlled VEGF gene expression.

The discovery that members of the ephrin (Eph) family are expressed differentially in arteries and veins from very early stages of development, before the development of functional circulation, was one of the first indications that artery–vein identity is intrinsically programmed.

Arterial endothelial cells express ephrin-B2, neuropilin-1 (NRP-1) [23], Notch, DLL4 and gridlock [24–27], while venous endothelial venous cells express NRP-2 and ephrin-B4, the receptor of ephrin-B2 [23, 28]. Mutations of Eph-B2 and of Eph-B4 both lead to early embryonic lethality around E9.5 [29–32]. Inhibition of the Notch signaling pathway leads to a decreased expression of arterial markers and ectopic expression of venous markers in arteries [24].

The collateral circulation takes place between arteries or arterioles, in most healthy tissues, and in pathological conditions, through an increase in vessel diameter after an ischemic injury [33]. In the collateral vessels, connecting two feed artery or the crowns of neighboring arterial trees, blood flow occurs in the opposite direction, resulting in a hemodynamic environment of low and oscillatory shear stress and inhibition of hemostatic thrombosis [34–36]. There are almost two different modalities of formation of collateral arteries: (*i*) artery-to-artery anastomosis bypass the capillary bed to provide blood flow to tissues served by an occluded artery. These connections show minimal tortuosity and do not increase their lumen after ischemic injury [37, 38]. Numerous connections have been demonstrated between branches of the same and of different coronary arteries in human hearts. Moreover, the circle of Willis connects major cerebral arteries at the base of the brain. Finally, the interconnections between the *a. thoracica interna* and the *a. epigastrica inferior* bypass any obstruction in the descending thoracic aorta down to the iliac artery; (*ii*) arteriole-to-arteriole anastomosis, interconnecting small portion of arterioles of neighboring arterial trees. They are present in most healthy tissues, as pial collaterals of the brain and spinal cord, skeletal muscle, skin, with an average diameter <100 μm [39], and in hearth, with an average diameter >150 μm [40], while they are absent in other tissues, as retina and non-capsular kidney [39]. They are tortuous [41–43] and their number, diameter and remodeling seem to be genetically determined [18, 35]. During embryonic development, microvascular collaterals develop after the arterial trees [35, 44]. These collaterals increase their diameter and wall thickness, as a consequence of the growth of a muscular

layer, while their number decrease. This is completed a few weeks after birth.

In physiological conditions, as a result of chronic exercise or muscle loading, there is an increase in the number and length of distal arterioles, with extension of an arterial tree [15]. In pathological conditions, arteriogenesis is associated to a degradation of the basal membrane, a modification of smooth muscle cells from a contractile to a proliferative phenotype associated with loss of desmin [45] and an inflammatory reaction around vessels. Therefore, the vessels are augmented in diameter and wall thickness [45–47].

Factors involved in angiogenesis and arteriogenesis

VEGF/VEGFR-2 signaling pathway controls endothelial cell function in both angiogenesis and arteriogenesis. Arterial differentiation occurs in angioblasts exposed to higher VEGF concentration, whereas angioblasts less exposed differentiate into venous vessels. In both developmental and adult arteriogenesis VEGF activation of extracellular signal regulating kinase 1/2 (ERK1/2) induces endothelial cell proliferation, network formation and increased vessel lumen size. The activation of this signaling is modulated by NRP-1 [48, 49] while TGF-α, VEGF, and FGF-2 stimulate angiogenesis through proliferation of endothelial cells, TGF-β, GM-CSF, monocyte chemoattractant protein-1 (MCP-1) and FGF-2 stimulate arteriogenesis through proliferation of smooth muscle cells [50]. FGF-2 and PDGF stimulate both angiogenesis and arteriogenesis. Kastrup *et al.* [51] demonstrated elevated levels of circulating angiogenic factors in ischemic injury (ischemic heart disease, stroke, or limb ischemia).

Pulsatile shear stress [52, 53] and circumferential stress [54] activates the cascade of events that leads to development of a collateral circulation [55–57]. Several genes are controlled by shear stress responsive elements in their promoter and fluid shear stress influences the expression of these genes [58].

The increased flow causes endothelial cell proliferation, with luminar expansion and release of platelet endothelial cell adhesion molecule (PECAM)-1 [59], MCP-1, intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1. Consequently, increased permeability of the endothelium, as indicated by the leakage of plasma proteins, erythrocytes and platelets into the vascular wall and the adherence of monocytes to the endothelium, were observed and recruitment of circulating monocyte, as well as resident macrophages [60], which in turn, promote arteriogenesis by their ability to secrete metalloproteinases, chemokines and growth factors [61, 62].

The upregulated expression of MCP-1 by endothelium attracts monocytes that adhere to and invade arteriolar collaterals. They, in turn, become activated, produce TNF-α and attract more monocytes [62]. Shear stress, stimulating arteriogenesis, increases the expression of an isoform of connexin, connexin-37, in endothelial cells [63, 64]. Moreover, connexin 37 is re-expressed in smooth muscle of growing collateral vessels.

Conflict of interests

There is no conflict of interests.

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