Plaque Angiogenesis Versus Compensatory Arteriogenesis in Atherosclerosis

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Many atherosclerotic lesions are vascularized by a network of capillaries that arise from the adventitial vasa vasorum. These capillaries may be important regulators of plaque instability. Reflecting their inflammatory microenvironment, the capillaries are immature endothelial tubes with disorganized branching, fragile and prone to rupture. The accumulation of erythrocytes after intraplaque hemorrhage may promote the transition from lesion stability to instability.2

Research interest in both angiogenesis and arteriogenesis, the maturation or de novo growth of collateral vessels,3,4 in atherosclerotic disease has intensified in recent years, reflecting the emerging success of antiangiogenesis strategies in cancer therapy. The bench-to-bedside milepost was reached in February 2004, when the US Food and Drug Administration approved bevacizumab (Avastin, Genentech), an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, for the treatment of colorectal cancer.5 It is controversial whether angiogenesis-targeted therapy holds similar promise in atherosclerotic disease.6 It must be remembered, however, that it has been 35 years since Folkman published his then-heretical hypothesis that tumor growth depended on angiogenesis,6 and 30 years since Brem and Folkman reported the first-known angiogenesis inhibitor.7 Many of the complex, multigene events of angiogenesis and arteriogenesis in atherosclerotic disease remain to be elucidated. The challenge is all the more difficult because of the diverse pathophysiological mechanisms of those two major kinds of new vascular growth associated with lesion development, one composed mainly of new capillaries, the other the collateral circulation formed by capillaries, arterioles, and arteries.2,4

Bochkov and colleagues in the current issue of Circulation Research distinguish new mechanisms of angiogenesis in atherosclerotic lesions.8 Lipoproteins accumulated in the extracellular space of the intima may be particularly susceptible to oxidative modification because they are not in contact with plasma antioxidants. It is generally agreed that heightened oxidative stress, characterized by lipid and protein oxidation in the vascular wall, is a key factor in atherosclerosis and the progression of atherothrombosis. A source of oxidized phospholipids is the phospholipids that reside in low-density lipoprotein (LDL). One of the most studied oxidized phospholipids, oxidized 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (OxPAPC), is a component of minimally modified LDL (MM-LDL).9 Two OxPAPC derivatives, 1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphorylcholine (POVPC) and 1-palmitoyl-2-glutaroyl-sn-glycero-3-phosphorylcholine (PGPC), have been located in both animal and human atherosclerotic lesions.9,10 The key and novel finding of the present study is upregulation of VEGF in both endothelial and mononuclear cells by OxPAPC, POVPC, and PGPC, as well as by several other oxidized phospholipids. The authors’ confirmation of their finding in an animal model suggests clinical significance. Overexpression of VEGF is known to increase capillary permeability11 and may be a primary cause of intraplaque hemorrhage.

In addition to upregulating VEGF, these oxidized phospholipids have been shown to play a role in regulating leukocyte–endothelial cell interactions and induction of inflammatory cytokines, such as IL-8, COX-2, and ADAMTS-1, from local endothelial cells, mononuclear cells, and macrophages.12,13 Beyond their angiogenic properties, IL-8 and COX-2 both exhibit a variety of proinflammatory properties, contributing to atherosclerotic progression.12 ADAMTS-1, a metalloprotease, can add to the proteolytic destabilization of plaque. ADAMTS-1 is upregulated in the intima when atherosclerosis is present, and its mRNA levels are significantly higher in proliferating/migrating cultured primary aortic smooth muscle cells (VSMC). It can cleave the large versican-containing proteoglycan population purified from cultured human aortic VSMC. Thus, ADAMTS-1 may promote atherogenesis by cleaving extracellular matrix proteins such as versican and promoting VSMC migration.14 Together, VEGF and oxidized phospholipids create a microenvironment composed of immature and hemorrhage-prone capillaries and cytokines that attract further inflammatory cell and oxidized lipid accumulation. The vicious cycle of the events makes lesions vulnerable, leading to eventual rupture. It is of note that fibroblast growth factor 2 (FGF2), another potent angiogenic factor, does not seem to play an important role, if any, in that inflammatory angiogenic response.

In contrast to plaque neovascularization, compensatory or collateral arteriogenesis is a physiological process in response to occlusion ischemia. When uninterrupted by angiostatic factors, the process usually results in the formation of mature vessels that can compensate for the loss of perfusion. The mechanisms of arteriogenesis are different from those of angiogenesis. Arteriogenesis originates in structural enlargement by growth of preexisting arteriolar connections into true

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collateral arteries. After bypassing the site of occlusion, the vessels have the ability to increase their lumen markedly by growth to provide enhanced perfusion to the jeopardized ischemic regions secondary to arterial occlusion. The proliferation of collateral arteries is not a process of passive dilatation but of active proliferation and remodeling. When an artery is occluded, blood flow can be redirected into preexisting arteriolar anastomoses, which experience increased mechanical forces such as shear stress and circumferential wall stress. The endothelium of the arteriolar connections is then activated, resulting in increased release of monocyte-attracting proteins as well as upregulation of adhesion molecules. The adherent monocytes promote arteriogenesis by supplying growth factors and cytokines, such as monocyte chemoattractant protein-1, granulocyte-monocyte colony-stimulating factor, and transforming growth factor-β1, which either attract or prolong the lifetime of monocytes. In concert, those effects of cytokines and growth factors efficiently enhance collateral artery growth, a result that cannot be achieved by application of the growth factors singly.15

Unlike in lesion neovascularization, where VEGF is the primary growth factor supporting the angiogenic process, compensatory arteriogenesis is orchestrated by several growth factors, among which FGF2 appears to be of crucial importance. As reported by Werner et al, in 104 patients with chronic total coronary occlusion, the FGF2 concentration in the collateralized arteries was higher than in the aortic root.16 FGF2, its concentrations highest in recent occlusions (2 to 12 weeks), which have the highest collateral resistance index, is the only growth factor that exhibits a close relation to the duration of occlusion and collateral function.16 FGF2 does not have a role in producing immature vessels with increased permeability, although that does not exclude VEGF’s participation in establishing a new vascular network that includes capillaries. Both FGF2 and VEGF are known for their ability to promote endothelial cell proliferation and migration and to stimulate tube formation by means of activation of the phosphatidylinositol 3-kinase/Akt signaling pathway.13,17 When delivered separately in a rabbit model, the FGF2 gene exceeded the VEGF gene in stimulating collateral arteriogenesis, but combined VEGF and FGF2 gene delivery produced additive or synergistic effects of collateral development.18 As recently reviewed by Heil and Schaper in this journal, the growth factors involved in arteriogenesis belong to the FGF family.19 This brings up the issue of differential effects of oxidized lipids on plaque vascularization and compensatory arteriogenesis.

As noted above, microenvironmental oxidized phospholipids upregulate VEGF expression in endothelial and mononuclear cells. In collateral arterial growth, the endothelial cells are not exposed to local phospholipids, but rather to oxidized or modified LDL in the circulation. In cultured endothelial cells, FGF2 is downregulated by copper-oxidized LDL via the platelet-activating factor (PAF) receptor.20 Whether modified LDL equivalent to copper-oxidized LDL exists in human plasma is debatable, but electronegative LDL isolated from human plasma has been shown to be mildly oxidized in vivo.21 L5, an extreme form of electronegative LDL present in hypercholesterolemic human plasma, can inhibit FGF2 transcription in vascular endothelial cells, leading to the cells’ apoptosis.22 The effects of L5 can be abolished by hydrolyzing the sn-2 residue with a PAF acetylhydrolase, suggesting an active role of PAF or PAF-like lipids accumulated in L5.22 Another difference between plaque neovascularization and compensatory arteriogenesis is the involvement of endothelial progenitor cells. In plaque neovascularization, the immature, likely pericyte-lacking capillaries arise from existing capillaries, and bone marrow–derived stem cells and endothelial progenitor cells do not appear to play a role. There is experimental evidence that circulating endothelial progenitor cells may participate in both endothelial regeneration and arteriogenesis.23 However, other evidence challenges that hypothesis. New findings are adding to the complexity of the mechanisms underlying plaque vascularization and compensatory arteriogenesis. The schematic provided (Figure) is much simplified.

Clearly, much research remains to be done to unravel neovascularization in atherosclerotic disease and its contribution to lesion progression and clinical events. It is hoped that progress such as that seen in the report by Bochkov and colleagues will lead to urgently needed novel therapies to counteract the devastating consequences of atherosclerotic disease. Perhaps one of the answers—and, as in the lead of
cancer research, in the near term—will be antiangiogenic cytokine therapy.

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References

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