INFLAMMATION AND ANGIOGENESIS

Michael Simons, MD
Beth Israel Deaconess Medical Center
Boston, Mass

The concept of ischemia as the primary stimulus of angiogenesis has been recently challenged on the basis of a number experimental observations. Thus, chronic reduction of myocardial ischemia with β-blockers has no effect on the development of collateral circulation in chronically ischemic pig, while many patients with advanced coronary demonstrate extensive neovascularization around the sites of epicardial coronary artery occlusions. At the same time, either direct or indirect measures of myocardial perfusion fail to document tissue ischemia at these sites. Other stimuli, such as shear stress and the presence of local inflammatory response, may be key factors involved in control of vessel growth in these settings.

The presence of a local “inflammatory” response is emerging as a particularly appealing possibility. Several experimental observations point to this mechanism. Thus, expression of monocyte chemotactant protein-1 (MCP-1) is induced in the endothelium of small venules immediately following reperfusion, and a local infusion of MCP-1 protein into an ischemic hindlimb resulted in enhanced collateral growth.1-3 Furthermore, the presence of blood-derived monocytes early after an acute MI was associated with increased expression of heparan sulfate-carrying core proteins4 that are involved in regulation of endothelial cell growth5; in contrast the absence of blood-derived monocytes is associated with decreased neovascularization.

The ability of macrophages to induce angiogenesis is hardly surprising given the wide variety of cytokines these cells are able to secrete, including VEGF, FGFs, TNFa, IL-6, and IL-8, among others. Studies in a rat acute infarct model suggest that infiltrating macrophages and not myocytes or endothelial cells are the predominant source of VEGF,6 and unlike other tissues,7 essentially all cardiac macrophages are of blood-derived (monocyte) origin.4,8 VEGF acts as a chemoattractant for macrophages9 and increases their adhesion to endothelial cells and the extracellular matrix proteins. Thus, a local administration (or production) of VEGF may lead to increased monocyte-macrophage influx followed by release of a number of cytokines including VEGF and bFGF, thus amplifying the original signal. In addition to the cytokine release, macrophages may also be an important source of NO generation that in turn can modulate growth factor signaling. In that regard, release of monocyte-derived TNF-α and interleukins will further contribute to generation of NO by stimulating eNOS in endothelial cells. These mechanisms may lie at the heart of VEGF-mediated induction of angiogenesis.

In addition to these well-described proteins, macrophages also secrete a cathelin-related proline-arginine rich peptide, PR39, that was originally isolated on the basis of antimicrobial activity from the pig intestine.10 The peptide is present in the wound fluid11 as well as along the border of acute myocardial infarction,4 and its appearance correlates with significant changes in heparan sulfate matrix.4,11 The peptide is able to rapidly cross cell membranes and has been reported to bind to SH3 domains of p47phox12 and p130Cas.13 Recent studies from our laboratory have demonstrated that the peptide is capable of inducing profound angiogenic response by inhibiting proteasome-dependent degradation of hypoxia-inducible factor (HIF)-1α. This in turn leads to a significant increase in expression of a number of angiogenesis-related genes including VEGF and VEGF receptors flk-1 and flt-1 as well as other proteins.14 The implications of these data will be discussed.

REFERENCES

Pathologic description

In normal vessels, the microvascular network of vasa vasorum is confined to the adventitial and outer media. In vessels with atherosclerotic involvement, these networks become more abundant and extend into the intima of lesions. Serial images taken during the perfusion of a silicone polymer through a human coronary artery show a narrowed lumen at the site of a plaque and later filling of multiple vessels that arise from vaso vasorum.

Putative functions of plaque neovascularization

1. The proliferation rates of endothelial cells in plaque vessels vary from 0% to 43%, which indicates these vessels are found in different stages of development. The presence of intimal neovascularization in lesions correlates with an increased proliferation index of all cell types, and suggests that they are markers of growing lesions.1

2. Intimal vessels are found in areas rich in macrophages, T cells, and mast cells-cell types that can activate angiogenesis. Their proximity to inflammatory infiltrates and the expression of adhesion molecules on the endothelium of plaque vessels both suggest that these vessels may recruit inflammatory cells into lesions and initiate a positive feedback mechanism that promotes inflammation in the vessel wall.2

3. Supply of oxygen and nutrients provided through plaque vessels and vaso vasorum may be necessary precondition for growth beyond a certain stage, after which diffusion from the artery lumen is insufficient to meet the metabolic demands of plaque tissue.

4. Plaque vessels may be a source of intraplaque hemorrhage. Plaque neovascularization is more prevalent in culprit lesions responsible for unstable angina, stroke or myocardial infarction. Factors that stimulate plaque angiogenesis may influence plaque stability.

Hypothesis

Angiogenesis associated with atherosclerotic lesions is a positive regulator of plaque growth and inflammation. We administered potent angiogenesis inhibitors to apolipoprotein E-deficient mice to determine if such treatments reduce plaque growth.3

Methods and results

Intimal capillaries were first demonstrated by immunohistochemistry staining for the endothelial cell markers CD31 and von Willebrand Factor (vWF) in advanced lesions of apoE/- mice.