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STATE-OF-THE-ART PAPER

The Role of Monocytes in Angiogenesis and Atherosclerosis

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New vessel formation inside the arterial wall and atherosclerotic plaques plays a critical role in pathogenesis of heart attacks and strokes. The 2 known mechanisms resulting in the formation of new vessels within the plaque are local ischemia and inflammation. Blood monocytes play an important role in both processes. First, they express receptors for vascular endothelial growth factor and some of them may serve as circulating ancestors of endothelial cells. Second, monocytes are associated with inflammation by synthesis of inflammatory molecules following their activation (e.g., after stimulation of Toll-like receptors). Neovascularization is a reparative response to ischemia, and includes 3 processes: angiogenesis, arteriogenesis, and vasculogenesis. Angiogenesis, the formation of new capillary vessels is known to occur in response to a hypoxic environment. The interaction between leukocytes and vascular wall via overexpression of various molecules facilitates the migration of inflammatory cells into the plaque microenvironment. Monocytes are intimately involved in tissue damage and repair and an imbalance of these processes may have detrimental consequences for plaque development and stability. Importantly, monocytes are comprised of distinct subsets with different cell surface markers and functional characteristics and this heterogeneity may be relevant to angiogenic processes in atherosclerosis. The aim of this review article is to present an overview of the available evidence supporting a role for monocytes in angiogenesis and atherosclerosis. (J Am Coll Cardiol 2014;63:1–11) © 2014 by the American College of Cardiology Foundation

Atherosclerosis is the primary cause for stroke and coronary artery disease in the Western World. It is a chronic inflammatory process characterized by development of lipid rich plaques within the layers of the arterial wall (Fig. 1). Within this thickened wall is where foam cells, monocyte derived lipid laden macrophages have been recognized (1). The formation of atherosclerotic plaque is a series of events that is initiated with lipid accumulation (fatty streak) followed by monocyte infiltration and the lipid core formation. Advanced lesions can obstruct arterial lumen, but at any stage atherosclerotic plaque may be complicated by rupture causing a hypoxia/ischemia of the downstream tissues and subsequent vascular complications.

Unhealthy lifestyles, diabetes, obesity, hypertension are still common contributors to the atherogenesis and development of unfavorable events thus prompting identification of new therapeutic targets (2). This is particularly true as current treatment modalities such not all patients are suitable for adequate coronary artery bypass grafting or angioplasty. Of interest, each of the risk factors mentioned previously triggers numerous pathological pathways involving a number of molecular processes, which include lipid metabolism, coagulation, apoptosis, hypoxia, and the immune response (3).

The body's natural response to ischemia is a reparative mechanism summarized by the term *neovascularization*. Neovascularization includes 3 processes: angiogenesis, arteriogenesis, and vasculogenesis. The formation of new capillary vessels, angiogenesis, has been extensively researched and occurs in response to a hypoxic environment (4). Progression and expansion of already existing collateral smooth muscle-type vessels or arteriogenesis, is believed to be a mechanism of organ preservation in the presence of vascular occlusion. Vasculogenesis or new vessel growth derived from progenitor/stem cells has been demonstrated in both the adult and embryo (5). Understanding these processes of vessel adaptation or formation is fundamental for developing new therapeutic strategies.

Inflammation has been shown to be an essential factor accompanying both the angiogenic and atherogenic pathways (5). Monocyte-derived macrophages play a pivotal role in lipid deposition and progression of atherosclerosis, but they are also implicated in the genesis of new vessels (6). The aim of this article is to present an overview of the available evidence supporting the role of monocytes in angiogenesis.

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Abbreviations and Acronyms

Ang = angiopoietin
β_2A = beta adrenergic system
bFGF = basic fibroblast growth factor
EPC = endothelial progenitor cells
HIF = hypoxia inducible factor
ICAM = intracellular adhesion molecule
IL = interleukin
MCP = monocyte chemoattractant protein
Tie = tyrosine kinase
TNF = tumor necrosis factor
VCAM = vascular adhesion molecule
VEGF = vascular endothelial growth factor

Search Strategy

We searched the following electronic databases (limiting the search from 1970 to July 2010): Pubmed, Medline, EMBASE, and Cochrane Reviews. Given the enormity of this subject area, we have focused on areas of particular relevance to angiogenesis and the role of monocytes in neovascularization. The key words used were *angiogenesis*, *neovascularization*, *vasculogenesis*, *angiopoietin*, *vascular endothelial growth factor* (VEGF), *Tie2*, *monocytes*, and *monocyte subsets*.

Atherogenesis and Plaque Neovascularization

Atherosclerosis is characterized by monocyte adherence to endothelium cell, migration into the arterial wall, and lipid accumulation (7). The earliest detectable atherosclerotic change is pathological intimal thickening (8).

Enlargement of the plaque results in intraplaque hypoxia that triggers the inflammatory cell infiltration, thus promoting local neovascularization (9). Interestingly, although intimal thickening is believed to be an early surrogate marker for atherosclerosis, pathological neovascularization is implicated in both early and late stages of the disease (9). For example, in experimental studies on hypercholesterolemia, adventitial neovascularization in the coronary arteries has been shown to be present even before the actual plaque (protrusion into the lumen) begins to develop (9). Two instrumental factors influencing the initiation of intra-arterial neovascularization are local ischemia and either local or systemic inflammatory burden. Pathological thickening of the intima greater than 100 μl increases the distance between the lumen and the inner parts of the vascular wall, thus impairing the supply with oxygen and nutrition. As vascular disease ensures excessive vessel wall thickness, proliferation of the vasa vasorum and intimal neovascularization is observed. Indeed, the degree of adventitial neovascularization has recently been demonstrated to be associated with intima-media thickness (10).

Evidence of the role of ischemia in the initiation of angiogenesis stems from the demonstration of increased levels of hypoxia inducible factor (HIF-1), which ultimately promotes VEGF production (4,11). As a potent stimulator of angiogenesis, VEGF is consequently able to create a local pro-angiogenic environment by mobilizing endothelial progenitor cells (EPCs) (Table 1) (12). Furthermore, aggressive plaque development and accelerated neovascularization of the vascular wall have been seen following the administration of VEGF in laboratory experiments (13).

Hypoxia-independent pathways triggered by an inflammatory stimulus within the vascular wall have also been

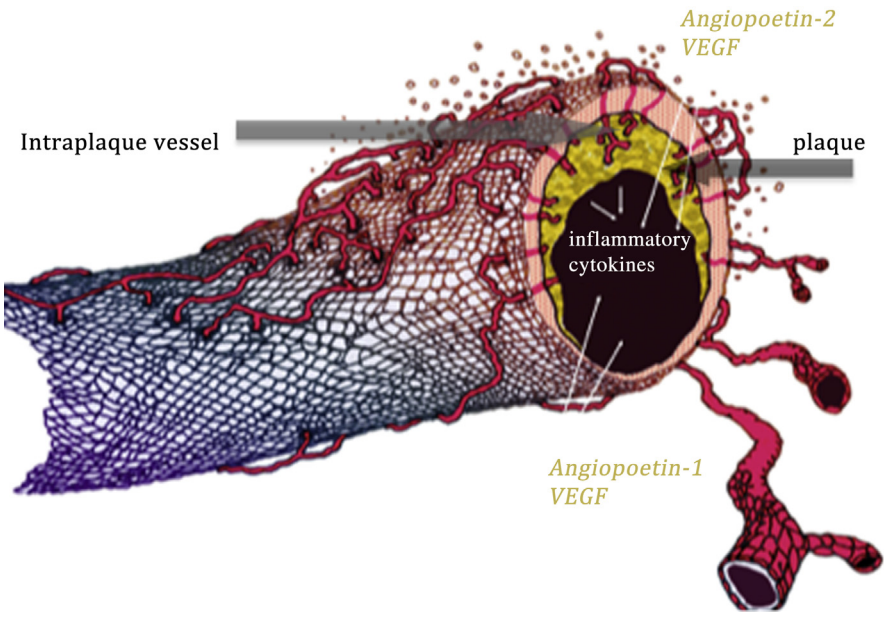

Figure 1 Angiogenesis and Inflammation

Site of occurrence within the arterial wall/vessel. VEGF = vascular endothelial growth factor.