Diversity of Denizens of the Atherosclerotic Plaque
Not All Monocytes Are Created Equal

Peter Libby, MD; Matthias Nahrendorf, MD, PhD; Mikael J. Pittet, PhD; Filip K. Swirski, PhD

The atherosclerotic plaque typically harbors cells of several lineages whose conversations, mediated by extracellular or cell surface–associated messengers, influence decisively the biology and clinical consequences of the lesion. Early vascular biology studies defined the resting state of the endothelium, characterized by the elaboration of antithrombotic and vasodilatory mediators. The activated endothelium recruits inflammatory leukocytes, favors clot accumulation, participates in angiogenesis, and can influence the behavior of subjacent smooth muscle cells in ways that favor atherogenesis and vascular constriction (Figure). More recently, we have come to appreciate that the endothelial cell not only can exhibit a spectrum of functions, but that some may arise postnatally from bone marrow–derived precursors.1 Thus, the heterogeneity of endothelial cells depends not only on the mutability of their function but also on their origin. The diversity of endothelium depends not only on lineage but also location, with increasingly well-understood differences between arterial, microvascular, and venous endothelial cells.

Smooth muscle cells also exhibit diversity (Figure). Phenotypic modulation of smooth muscle cells, from those rich in contractile elements and quiescent to those that acquire more fibroblastoid features such as heightened extracellular matrix synthesis, migration, and proliferation, characterizes atherogenesis.2 Smooth muscle cells that invest the walls of different arteries derive from distinct germ layers and embryonic precursors. As in the case of endothelial cells, smooth muscle cells in arterial hyperplastic lesions such as atheroma can also arise from bone marrow precursors.3,4

Activated endothelial cells recruit leukocytes to nascent atheroma. Among the leukocytic cell types captured by the endothelium, we have detailed knowledge of the T lymphocyte, now known to exert important regulatory influences on the other cells that congregate in the lesions. The functional diversity of T-cell subtypes influences many chronic inflammatory diseases, atherosclerosis included (Figure). Th1 cells and their signature mediators drive atherothrombosis. Products of Th2 cells can mitigate inflammation and may mute atherogenesis.5 Regulatory T cells may have a special role in promoting plaque rupture and thrombosis.6 Mononuclear phagocytes by far outnumber T lymphocytes in the typical atheroma. These foot soldiers of the inflammatory response appear to follow commands issued from the less-abundant lymphocytes. Hints on diversity in macrophages that populate atheroma have surfaced over the years. Only a subpopulation of macrophages appears to express the potent procoagulant tissue factor, a common trigger of arterial thrombosis.7 Likewise, a pool of polymorph-like macrophages in plaques contains myeloperoxidase and “neutrophil” elastase.8,9 We long ago described selectivity in gene expression in lesional macrophages.10 Whether functional subpopulations of macrophages arise from differential stimuli encountered in regions of the plaque (eg, from T cells) or might reflect lineage predispositions that depend on programming before penetration into the plaque has remained an open question. Recent work has begun to shed new light on this unresolved aspect of the inflammatory pathways that critically influence plaque biology.

In 2007, 2 groups simultaneously and independently reported that hypercholesterolemic mice exhibit a profound shift in their populations of peripheral blood monocytes, as defined by a surface marker of as-yet-uncertain functional significance known as Ly-6C or 6r-1 (Figure).11,12 The normocholesterolemic mouse has approximately equal numbers of circulating monocytes bearing low or high levels of this marker (Ly6Clo and Ly6Chil subsets). After consumption of an atherogenic diet, the Ly6Chil population rises exponentially. In mice that lack apolipoprotein E and hence have susceptibility to diet-induced hyperlipidemia and atherosclerosis, cells bearing high levels of Ly-6C accumulate in plaques preferentially. Multiple mechanisms seem to promote the prominence of Ly6Chil cells in peripheral blood and plaques. Many indications point to cells of the Ly6Cil subset as particularly proinflammatory (Table).13 Notably, the Ly-6Chil cells contain higher levels of myeloperoxidase, certain proteinases, and proinflammatory cytokines such as tumor necro-
sis factor \( \alpha \). Emerging data in the mouse show important and divergent functional roles for the Ly-6Clo and Ly-6Chi subsets in other conditions such as the healing of myocardial infarction and visceral adiposity. The application of these concepts to human disease has lagged, in part because of the lack of consensus on the human correlates of the subsets conveniently defined in mice by the Ly-6C marker. Human monocytes do not express Ly-6C or an evident homolog, leaving the field a bit unsettled about how to translate the exciting results in mice to our human patients.

In the current issue of *Circulation*, An et al provide data that promise to help us out of this translational quandary and, more fundamentally, furnish new functional insight into how the inflammatory subset of blood monocytes may selectively accumulate at sites of endothelial activation and thrombosis. These workers provide evidence that the P-selectin glycoprotein ligands track with Ly-6C in mouse mononuclear phagocytes, and very importantly lend support to the notion that the CD16 population of mononuclear cells may selectively accumulate at sites of endothelial activation and thrombosis. These workers provide evidence that the P-selectin glycoprotein ligands track with Ly-6C in mouse mononuclear phagocytes, and very importantly lend support to the notion that the CD16 population of mononuclear cells represents a proinflammatory population of monocytes in humans. Activated endothelial cells elevate expression of the leukocyte adhesion molecule P-selectin. Elegant work by Denisa Wagner and her colleagues has defined a role for P-selectin in leukocyte recruitment to sites of inflammation in experimental atherogenesis. Platelets, once activated, exteriorize preformed P-selectin, increasing their adhesivity to activated endothelium and probably promoting the stability and propagation of thrombi. Thus, P-selectin on endothelial cells may recruit selectively the inflammatory subset of mononuclear phagocytes to sites of early atherogenesis, and P-selectin exteriorized and released locally by activated platelets may recruit and retain particularly proinflammatory populations of monocytes at sites of thrombosis. The activated platelet also exteriorizes and releases locally the potent macrophage agonist CD40 ligand, previously shown by us to promote progression of experimental atheroma and to induce tissue factor production by monocyte/macrophages.

The more we learn, the more we appreciate the importance of heterogeneity of cells in the plaque. Monocytes have now joined their brethren in the atheroma as deriving from precursors of diverse origin as well as acquiring different function palettes in response to local signals. The work of the Oklahoma group reported here represents a major boost to our understanding of the functions of the recently identified proinflammatory pool of mononuclear phagocytes. Moreover, their discovery provides us with a powerful tool to probe the role of this cell population in the pathogenesis of human diseases. The recognition of this heterogeneity in the phagocytes in plaques also points to strategies that target selectively the recruitment or matu-

Table. Monocyte Subsets Preferentially Express Certain Effector Functions

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ration of the proinflammatory subset as a new avenue for the therapy of atherosclerosis and its complications.

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None.

**References**


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