Monocyte Fate in Atherosclerosis

Ingo Hilgendorf, Filip K. Swirski, Clinton S. Robbins

Abstract—Monocytes and their descendant macrophages are essential to the development and exacerbation of atherosclerosis, a lipid-driven inflammatory disease. Lipid-laden macrophages, known as foam cells, reside in early lesions and advanced atheromata. Our understanding of how monocytes accumulate in the growing lesion, differentiate, ingest lipids, and contribute to disease has advanced substantially over the last several years. These cells’ remarkable phenotypic and functional complexity is a therapeutic opportunity: in the future, treatment and prevention of cardiovascular disease and its complications may involve specific targeting of atherogenic monocytes/macrophages and their products. (Arterioscler Thromb Vasc Biol. 2015;35:272–279. DOI: 10.1161/ATVBAHA.114.303565.)

Key Words: atherosclerosis ■ cardiovascular disease ■ inflammation ■ macrophage ■ monocyte

Cardiovascular and cerebrovascular diseases are the leading cause of morbidity and mortality worldwide.1 The main cause of vascular disease is atherosclerosis or build-up of plaque in the arteries. Myeloid cells are key cellular protagonists of the inflammatory response that drives atherogenesis.2,3 Circulating monocytes adhere to the activated endothelium, infiltrate the vessel wall, become lesional macrophages, and participate decisively in the development and exacerbation of atherosclerosis. In this brief review, we discuss the current understanding of monocyte biology in atherosclerosis.

Monocytes Are Protagonists of Atherosclerosis

Renewed interest in monocyte biology began with the subdivision of monocytes into 2 main subsets.4 In mice, monocytes can be distinguished based on their cell surface expression of the glycoprotein Ly6C. Ly6C<sup>high</sup> monocytes—CD14<sup>+</sup>CD16<sup>+</sup> and CD14<sup>+</sup>CD16<sup>+</sup> cells in humans—are short-lived, transport tissue antigens to lymph nodes,5 and accumulate at sites of inflammation<sup>4</sup> where they differentiate to macrophages and dendritic cells. Ly6C<sup>low</sup> monocytes—CD14<sup>+</sup>CD16<sup>+</sup> monocytes in humans—are longer lived, patrol the vasculature, respond early to infection,<sup>6</sup> and survey endothelial integrity.<sup>7</sup> Sophisticated fate mapping studies recently confirmed a long-held theory that Ly6C<sup>low</sup> monocytes arise from circulating Ly6C<sup>high</sup> cells.<sup>8–10</sup>

In humans, classical CD14<sup>+</sup>CD16<sup>+</sup> monocytes similarly convert to CD14<sup>+</sup>CD16<sup>+</sup> nonclassical monocytes through a CD14<sup>+</sup>CD16<sup>+</sup> monocyte intermediate.<sup>11</sup> Monocytes are essential to the development and exacerbation of atherosclerosis. As disease worsens, the number of Ly-6C<sup>high</sup> monocytes in the blood rises.<sup>12–14</sup> A large body of evidence shows that in addition to increasing in number, Ly-6C<sup>high</sup> monocytes preferentially adhere to activated endothelium, infiltrate the vessel wall, and become lesional macrophages. The role of Ly6C<sup>low</sup> monocytes in atherosclerosis progression is less clear. Although able to ingest oxidized lipoproteins,<sup>15</sup> Ly6C<sup>low</sup> monocytes do not contribute directly to the lesional macrophage pool.<sup>10,16,17</sup>

Atherosclerosis is aggravated in Nur77-deficient mice—which lack Ly6C<sup>low</sup> monocytes<sup>19</sup>—in some studies, but not in others.<sup>16,17,19</sup> Interpreting these data is further complicated by the function of Nur77 in other processes, including the regulation of macrophage polarization and TLR signaling pathways.

In humans, studies suggest that circulating monocyte levels predict cardiovascular risk. In a large prospective cohort of 951 patients undergoing elective coronary angiography, increased numbers of intermediate CD14<sup>+</sup>CD16<sup>+</sup> monocytes independently predicted cardiovascular death, myocardial infarction (MI) and stroke over a period of 2 and a half years.<sup>20</sup> In a general population (n=659) with no known cardiovascular disease, increased numbers of classical CD14<sup>+</sup>CD16<sup>+</sup> monocytes in the blood predicted cardiovascular events within a mean 15-year follow-up independently of sex, age, and classical cardiovascular risk.
Long-term follow-up studies have shown that within the first week after acute MI, elevated levels of classical and intermediate monocytes are associated with decreased left ventricular function and larger infarct size. Furthermore, preferential accumulation of CD14++CD16- cells in the infarct border zone has been observed in the myocardium of patients that succumb to acute MI. Increased mobilization and recruitment of classical monocytes into the heart may be attributed to the monocyte chemotactic factor, monocyte chemotactic protein 1, whose levels are increased in acute coronary syndrome and is associated with increased cardiovascular mortality.

Long-term follow-up studies have shown that within the first week after acute MI, elevated levels of classical and intermediate monocytes are associated with decreased left ventricular function for ≤6 months. Moreover, compared with cells in patients with stable coronary artery disease, circulating classical monocytes are more adhesive and increase in number in patients with heart failure. Assessing nonculprit coronary plaque size in 90 acute MI patients during the acute phase and 7-month later found that peak monocyte counts in the blood independently predicted plaque progression after ST-elevation MI. Intravascular optical coherence tomography of nonculprit lesions in patients with unstable angina showed that increased fibrous cap thickness—a measure of plaque stability—inversely correlated with an increased CD16- (nonclassical and intermediate) blood monocyte fraction during a 9-month follow up. In a 5-year follow up of 255 ST-elevation MI patients, the peak blood monocyte count after infarction also predicted major adverse cardiac and cerebrovascular events, including cardiac death, sudden death, nonfatal MI, unstable angina, and stroke.

Is there any evidence that targeting monocytes in patients with cardiovascular disease is therapeutically beneficial? Anti-platelet treatment reduces monocyte–platelet aggregation, a process thought to promote atherogenesis in patients with acute coronary syndrome. In addition to lowering cholesterol levels, life-saving statin therapy attenuates the production of inflammatory cytokines and coagulant factors and decreases the expression of cell adhesion molecules by circulating monocytes in hypercholesterolemic patients. Angiotensin-converting enzyme inhibitors reduce tissue factor and serum levels of monocyte chemotactic protein 1 in patients after acute MI, decelerating the coagulation-inflammation-thrombosis cascade. Furthermore, addition of the renin inhibitor aliskiren suppresses circulating numbers of classical monocytes and increases myocardial salvage after acute MI. A direct role for monocytes in the progression of coronary artery disease was recently observed in a prospective, placebo-controlled phase II clinical trial assessing the effects of intravenous administration of liposomal alendronate (LABR-312, Biorest) on percutaneous coronary intervention and stenting. Monocytes and macrophages are transiently depleted after the uptake of LABR-312 liposomes as a result of intracellular accumulation of toxic levels of bisphosphonates and the induction of apoptosis. Strikingly, diabetic patients and those with elevated monocyte counts responded to treatment with reduced in-stent restenosis for ≥6 months. Collectively, these studies suggest an association between increased cardiovascular disease risk and elevated levels of circulating classical and intermediate monocytes. Improved clinical outcome is associated with treatment regimens that reduce monocytosis.

### Monocyte Production, Mobilization, and Accumulation in Developing Lesions

Monocytes arise from proliferating and differentiating hematopoietic stem and progenitor cells in the bone marrow. Hematopoietic stem cells progress through increasingly committed progenitors, the most restricted toward the monocyte lineage being common monocyte progenitor cells. Increased production of bone marrow monocytes in experimental models of atherogenesis has been reported in hypercholesterolemic swine, rabbits, and rodents. More recently, it was shown that hypercholesterolemia also induces monopoiesis in extramedullary organs, including the spleen. During atherosclerosis, medullary and extramedullary monopoiesis are regulated by the growth factors granulocyte macrophage–colony stimulating factor and interleukin 3. Cell intrinsic factors also influence hypercholesterolemia-associated monopoiesis. Proteoglycan-bound apolipoprotein E on the surface of hematopoietic stem and progenitor cell (HSPC) promotes cholesterol efflux via the ATP-binding cassette transporters ATP-binding cassette transporter 1 and ABCG1. Genetic deficiencies in the reverse cholesterol transport machinery results in increased plasma membrane lipids and upregulation of the common β chain of the interleukin-3/granulocyte macrophage–colony stimulating factor receptor. Notably, infusion of high-density lipoprotein and Liver-X Receptor agonists in this setting restores reverse cholesterol transport and reduces hypercholesterolemia-induced hematopoietic stem and progenitor cell proliferative responses. In the clinical setting, familial hypercholesterolemia is similarly associated with blood monocytosis.

Bone marrow HSPC mobilization to peripheral tissues occurs in many inflammatory contexts. In experimental atherogenesis, extramedullary monopoiesis is driven by HSPC mobilization. Although the mechanisms that regulate HSPC exit from the bone marrow remain incompletely understood, HSPC mobilization after MI is regulated by β3-adrenergic receptor signaling and downregulation of the HSPC homing and retention factor CXCL12. It was recently shown that accelerated myelopoiesis associated with chronic stress is similarly regulated by the sympathetic nervous system. Mobilization of monocytes from the bone marrow is also regulated by chemokine/chemokine receptor interactions. C-C chemokine receptor (CCR)2 blockade in murine models of atherogenesis, for example, impairs monocyte exit from the

### Nonstandard Abbreviations and Acronyms

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<th>Abbreviation</th>
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<tr>
<td>CCL</td>
<td>chemokine (C-C motif) ligand</td>
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<td>CCR</td>
<td>C-C chemokine receptor</td>
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<tr>
<td>CD</td>
<td>cluster of differentiation</td>
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<tr>
<td>HSPC</td>
<td>hematopoietic stem and progenitor cell</td>
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<td>Msr1</td>
<td>type 1 macrophage scavenger receptor class A</td>
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bone marrow and is associated with a dramatically reduced atherosclerosis burden.55 Consistent with these observations, MI leads to the production of MCP-3/CCL7 (chemokine (C-C motif) ligand 7), another ligand of CCR2, by B lymphocytes, which regulates mobilization of Ly6C<sup>high</sup> monocytes from the bone marrow into the ischemic myocardium.56

The trafficking of monocytes into atherosclerotic lesions is dependent on several chemokine/chemokine receptor interactions. Numerous studies have demonstrated the importance of CCR2/MCP-1, CX3CR1/fractalkine, and CCR5/CCL2/CCL5 interactions in the progression of experimental atherosclerosis.14,55,57 Although CCL2 may predominantly affect monocyte mobilization from the bone marrow, CCL5 and CXCL1 directly attract monocytes to atherosclerotic lesions.58 CCL20 mobilizes as well as recruits Ly6C<sup>high</sup> monocytes to plaques through interactions with CCR6.69 Additionally, CX1R1 signaling in monocytes and macrophages supports cell survival.60

Monocytes accumulate in plaques at sites of endothelial dysfunction/activation—areas associated with increased expression of cell adhesion molecules, including endothelial vascular cell adhesion molecule-1.61 Platelets and neutrophils also facilitate monocyte recruitment into plaques (Figure). Platelet binding of the endothelium precedes the appearance of leukocytes in plaques62 and induces bidirectional expression of adhesion molecules and the production of monocyte attracting chemokines.63 P-selectin glycoprotein ligand-1/P-selectin interactions mediate binding of monocytes to endothelial cells as well as platelets.64,65 Degranulation and surface expression of P-selectin increases on platelet activation, enabling monocyte–platelet aggregation. Aggregated platelets release chemokines (eg, CCL5, CXCL4) and cytokines (eg, interleukin1β), whereas monocytes increase integrin activity and expression of inflammatory mediators (eg, CCL2, tumor necrosis factor α, tissue factor), further propagating monocyte recruitment to lesions.66 Neutrophils promote monocyte recruitment into atherosclerotic lesions by producing cathelicidin, which binds formyl-peptide receptor 2 on Ly6C<sup>high</sup> monocytes, inducing integrin activation.67,68

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**Figure.** Monocyte action and interaction in atherosclerosis. Ly6C<sup>high</sup> monocyte are recruited to activated endothelium guided by chemokines. Interaction with platelets and neutrophil-derived CRAMP stimulates surface expression of adhesion molecules, thereby facilitating attachment and extravasation. Ly6C<sup>high</sup> monocytes in the lesion can directly contribute to plaque inflammation, differentiate into proliferating lesion macrophages, exit the plaque, for example, via the lymphatics for antigen presentation in draining lymph nodes or die locally. In the circulation, Ly6C<sup>high</sup> monocytes convert into Ly6C<sup>low</sup> monocytes that patrol the vasculature. When detecting endothelial damage in a CX3CR1- and TLR7-dependent manner, Ly6C<sup>low</sup> monocytes attract neutrophils that induce focal endothelial necrosis for subsequent disposal of the cellular debris by Ly6C<sup>high</sup> monocytes. Dashed arrows depict spatial relationship; solid arrows depict developmental and functional relationships. ROS indicates reactive oxygen species; and SR, scavenger receptors.
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During the development and exacerbation of atherosclerosis, monocytes infiltrate the vessel wall and become lesional macrophages. Macrophages ingest oxidized lipoproteins via scavenger receptors and, as lipid-rich foam cells, contribute to the physical bulk of developing plaques. These insights have contributed to the perception that macrophage accumulation results from the continuous recruitment of blood monocytes. However, it has recently been shown that in some inflammatory contexts, the accumulation of tissue macrophages may not depend on monocyte recruitment. The adventitia also harbors hematopoietic progenitors, suggesting additional explanations for how atherosclerosis evolves. Our recently published data shows that lesional macrophage accumulation also depends on considerable proliferation of macrophages locally within the developing plaque.

Macrophage proliferation in atherosclerotic lesions has been observed in humans, rabbits, and mice. In vitro studies have also shown that macrophages can proliferate in response to oxidized low-density lipoprotein. It is surprising then how little is known about the role proliferation plays in plaque growth. Using parabiosis, a surgical procedure that allows joining and exchange of circulations between congenic mouse strains, the relative importance of monocyte influx versus macrophage proliferation to plaque development was recently assessed. Local proliferation, it was shown, accounted for \( \approx 90\% \) of macrophage accumulation in established disease. In contrast, monocyte recruitment played a much larger role in lesion development during early atherosogenesis. Therefore, understanding the complexity of atherosclerosis progression will necessitate determining the relative contribution of proliferation versus monocyte recruitment to plaque growth during different stages of disease. The balance between them may be crucial to plaque development and stability. The data suggest that as atherosclerosis progresses, lesional macrophage accumulation depends increasingly on local proliferation rather than monocyte influx. Our study also reconciles some of the conflicting data in the field. On the one hand, monocyte influx is absolutely necessary to atherosclerosis: in the absence of colony stimulating factor, but is mediated by the type 1 scavenger receptor. Macrophages with targeted deletion of Msr1 uptake oxidized low-density lipoprotein poorly in vitro. In addition, Msr1-mediated internalization of lysophosphatidylcholine, a phospholipid component of oxidized low-density lipoprotein, induces proliferation in peritoneal macrophages in vitro.

Our recently published in vivo data shows that Msr1 promotes local macrophage proliferation within developing plaques. Additional work is required to determine whether lesional macrophage proliferation is a general feature of scavenger receptor activity or regulated by Msr1 alone. Macrophage receptor with collagenous structure is another class A scavenger receptor with considerable homology to Msr1, but whose role in atherosclerosis is not known. CD36 is a class B scavenger receptor that has been implicated in the development of necrotic lesions in advanced atherosclerosis. Although CD36 promotes vascular smooth muscle cell proliferation and induces neointimal hyperplasia, its role in regulating macrophage proliferation is unknown.

In vitro studies establish that macrophages can be classified into functionally distinct subsets. Functional polarization is also observed in vivo under physiological and pathological conditions. Macrophages undergo either classical M1 or alternative M2 activation, although other subsets have been described. M1 macrophages express high levels of inflammatory cytokines, increased production of reactive nitrogen and oxygen intermediates, and promote Th1 responses. M2 macrophages participate in tissue remodeling, wound healing, and immune regulation; are highly phagocytic; express high levels of scavenging molecules, mannose, and galactose receptors; and produce ornithine and polyamines through the arginase pathway. The functional profile of macrophages in atherosclerotic disease is poorly understood, but is likely influenced by their responsiveness to the microenvironment. Our unpublished data suggest that macrophages within atherosclerotic lesions comprise a spectrum of M1- and M2-like phenotypes. Notably, our data suggest polarization within the developing plaque influences macrophage function. Proliferation profoundly alters the transcriptional profile of lesional macrophages, as well as increases macrophage expression of inflammatory mediators, including interleukin-12 and inducible nitric oxide synthase (NOS2; Robbins and Hilgendorf, unpublished observations). Therefore, proliferation adds not only to the physical bulk of the plaque, but may promote inflammation through expansion and polarization of macrophages toward an inflammatory M1 phenotype.

Is macrophage proliferation a protective response to increase the number of cells capable of sequestering lipids? Alternatively, proliferating macrophages may be more inflammatory than nonproliferating macrophages, more susceptible to apoptosis, and contribute to lesion bulk. Given the importance of macrophage proliferation, it is necessary to re-evaluate the role of monocyte recruitment? Perhaps monocytes...
contribute to atherosclerosis independent of their function as macrophage precursors. Jakubzick et al recently demonstrated that during steady state conditions, Ly6C\textsuperscript{high} monocytes differentiate minimally as they transport antigens from peripheral tissues to draining lymph nodes.\textsuperscript{3} Ly6C\textsuperscript{low} monocytes patrol the vasculature scavenging debris and maintain endothelial integrity during inflammation.\textsuperscript{6,7} We have shown that during atherosclerosis, undifferentiated monocytes entering developing lesions produce inflammatory cytokines, proteolytic enzymes, and reactive oxygen species.\textsuperscript{36}

For decades, it was believed that tissue macrophages derive exclusively from bone marrow progenitors and their monocyte descendants.\textsuperscript{107} However, recent studies show that in many tissues, resident macrophages originate embryonically from the primitive yolk sac, independent of hematopoietic stem cells and circulating monocytes and are maintained in adulthood by in situ proliferation.\textsuperscript{70,108–110} The function of tissue-resident macrophages in adult tissue, however, is not yet clear. It remains to be determined whether yolk sac macrophages colonize the artery wall, and if so, what their contribution might be to inflammatory responses in atherogenesis.

Monocytes and their descendant macrophages are essential to the development and exacerbation of atherosclerosis, a lipid-driven inflammatory disease. Our understanding of how monocytes accumulate in the growing lesion, differentiate, ingest lipids, and contribute to disease has advanced substantially over the last several years. However, important questions in monocyte/macrophage biology in atherosclerosis remain to be answered. What contributes more to disease progression, monocyte influx, or—as our recent work suggests—local macrophage proliferation? What are the relative numeric and functional contributions of each process to disease progression? How does the balance between the 2 processes change with age, diet, comorbidities, therapy? Does one process influence the other? Which of the 2 is the better therapeutic target? These questions are significant to human health because they are critical to understanding and addressing the pathophysiology of atherosclerosis. According to our observations, caution is required, and additional and alternative approaches should be explored.

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Disclosures
None.

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outcome in patients with chronic kidney disease. 

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Significance
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