Monocytes and macrophages are abundantly present in both human atherosclerotic plaques and lesions obtained from animal models. Direct evidence for the importance of monocytes in atherogenesis could be demonstrated in a study where their depletion reduced the plaque formation in rabbits. Three principal monocyte subsets (named classical, intermediate, and nonclassical) have been described in mice and man. In humans, monocytes can be differentiated based on the expression of CD14 and CD16. Classical monocytes are defined as CD14+CD16−, intermediate monocytes as CD14++CD16+, whereas nonclassical monocytes are CD14+CD16+. In mice, CD115+ monocyte subsets are mainly discriminated based on the expression of lymphocyte antigen 6C (Ly6C) but also CD43. Monocytes being Ly6C++CD43+ are CX3CR1lowCCR2high and thought to correspond to human classical monocytes. In contrast, murine Ly6C+CD43++ monocytes being CX3CR1highCCR2low are phenotypic equivalents of human nonclassical monocytes. Of note, although yet unconfirmed, a recent study provides evidence for classical monocytes to be of dominant importance in atherogenesis and progression as compared with their nonclassical counterparts in mice.

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Chemokines Control Monocyte Homeostasis Under Steady State and in Hypercholesterolemia

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contribute to arterial monocyte accumulation. Under steady-state conditions, classical monocyte homeostasis is tightly regulated by the CCL2/CCR2 axis and mice deficient for CCR2 display severely reduced counts of circulating classical monocytes. Under acute inflammatory conditions, murine classical monocytes are mobilized from the bone marrow in a CCL2/CCR2- and CCL7/CCR2-dependent fashion. However, in the context of atherosclerosis, these axes seem to be of minor relevance as plasma concentrations of CCL2 and CCL7 do not increase in apolipoprotein E–deficient (Apoe<sup>−/−</sup>) mice fed a high-fat diet. Furthermore, although mice deficient of CCR2 display a markedly reduced number of circulating classical monocytes already under steady-state conditions, monocyte counts in these mice do still increase under hypercholesterolemia. Instead, the CXCL1/CXCR2 axis has been unraveled to be of major importance in classical monocytosis induced by high-fat diet as plasma CXCL1 increases under such conditions and CXCL1 neutralization abrogates expansion of circulating classical monocytes. As a consequence, injection of CXCL1 neutralizing antibodies reduces lesional macrophage counts and resulting lesion sizes are smaller.

Beside direct mobilization of classical monocytes from the bone marrow, a more recent study links cholesterol efflux via ATP-binding cassette transporters with hematopoietic stem and multipotential progenitor cell mobilization and extramedullary proliferation. This might be of high interest as the spleen has been identified as reservoir for classical monocytes, which can be readily mobilized during inflammation. In accordance with this finding, splenectomized mice failed to develop a monocytosis under acute inflammatory conditions and splenic monocytes give rise to lesional macrophages. Of note, several chemokines, including CCL3 and CXCL8, have been shown to suppress hematopoietic stem and multipotential progenitor cell proliferation and may thus potentially counteract hematopoiesis under conditions of hypercholesterolemia.

**Chemokines Lure Monocytes Into Atherosclerotic Lesions**

Ligation of chemokine receptors sets off a signaling cascade resulting in chemotraction and integrin activation, a step of crucial importance in firm arrest of monocytes on activated endothelium. An important chemokine in monocyte attraction is CCL2. Almost 20 years ago it has been reported that mice deficient for CCR2 exhibit severely reduced atherosclerotic lesions. However, with the critical importance of CCL2 in...
monocyte mobilization from sites of production, the lesion phenotype observed in CCR2-deficient mice may be ascribed to low circulating monocyte numbers rather than inhibited recruitment.6

The majority of chemotactic molecules is derived from circulating platelets and neutrophils or from tissue resident cells such as endothelial cells and macrophages. In fact, the importance of platelets in atherosclerosis30,31 may in part be explained by the delivery and deposition of monocyte attracting chemokines. Platelets are rich in cationic arrest chemokines such as CCL5 (RANTES), CXCL4 (PF4), and CXCL7.22 Recent work highlights the importance of CCL5 in the recruitment of classical monocytes.6,23 Herein, platelets deposit CCL5 along the endothelium of atherosclerotic lesions.31 Immobilized CCL5 is recognized by rolling monocytes involving both CCR1 and CCR5. Interestingly, the interaction of CCL5 with its receptors requires sialylation of the receptors hereby creating favorable conformational changes in Ccl5 receptors or enforcing electrostatic interactions of basic chemokine residues with negatively charged sialic acids attached to the chemokine receptors.24 Hence, mice lacking St3Gal-IV exhibit drastically reduced arterial monocyte adhesion and vastly diminished atherosclerotic lesion sizes.25 The suitability of CCL5 receptors as therapeutic targets becomes evident in studies where global blockade of CCL5 receptors using Met-CCL5,26 inhibition of CCR5 with maraviroc,27 or CCR5 deficiency28 lead to reduced atherosclerotic lesion sizes and lower lesional macrophage contents. With the acceleration of atherosclerosis in response to myocardial infarction,29 it is interesting to note that a recent clinical study evidenced a correlation between plasma CCL5 levels and progression of atherosclerosis after acute coronary syndrome.30 Finally, CCL5-evoked arterial monocyte adhesion can further be enhanced when CCL5 interacts with CXCL4.31 The in vivo relevance of this synergistic interaction was substantiated by findings that disruption of CCL5–CXCL4 heteromer formation markedly inhibited atherosclerotic lesion formation.31

Lesional cells release chemokines controlling monocyte adhesion and transmigration, where ligands of CXCR2 may have a dominant importance. CXCL1 (KC in mice, GROα in humans) has been detected in aortic valve sections from atherosclerotic mice32 and recently, a connection between oxidized low-density lipoprotein (oxLDL) and endothelial CXCL1 release has been established.33 Herein, oxLDL requires the lysophosphatidic acid–generating enzyme autotaxin as well as lysophosphatidic acid receptors 1 and 3 to induce release of CXCL1 from endothelial cells as well as subsequent monocyte adhesion. Evidence for the role of CXCR2 in atherosclerosis mainly stems from studies using bone marrow chimeras. Indeed, lack of CXCR2 in hematopoietic cells protects from atherosclerosis and reduces arterial macrophage contents.34 Similar effects have been observed in atherosclerotic mice deficient for CXCL1.35 Interestingly, it was shown that CXCR2 is more important for macrophage accumulation in established lesions than its ligand CXCL1 alone,32 suggesting the importance of alternative CXCR2 ligands. In this context, migration inhibitory factor (MIF) has emerged as important ligand of CXCR2-mediating arterial monocyte recruitment.35 MIF can be released from macrophages in response to oxLDL and from endothelial cells under hypoxia.36 In addition, MIF has recently been shown to be released from NG2+ pericytes in the microcirculation, thus guiding leukocytes to sites of inflammation.37 Besides blocking MIF to induce plaque regression and to inhibit macrophage accumulation,38 gremlins-I has recently been identified as an endogenous inhibitor of MIF. Administration of a recombinant fusion molecule nGremlin-Fc that binds to MIF substantially reduced atherosclerotic lesion sizes and arterial macrophage contents.38 Beyond MIF and CXCL1, CXCR2 also recognizes other chemokines such as CXCL2, 6 or 7. Although CXCL5 seems to be important during foam cell formation (see below), the role of the other CXCR2 ligands in atherosclerosis with regard to effects on monocytes requires further studies.

## Chemokines Regulate the Fate of Monocytes Within Atherosclerotic Lesions

Within the plaque, monocyte-derived macrophages are surrounded by a multitude of chemokines, all of which differentially modulate fate of macrophages with respect to activation, proliferation, survival, and polarization. Scavenger receptors (eg, CD36, SRA1) are involved in the uptake of modified LDL by macrophages and are important players in foam cell formation. The transmembrane chemokine CXCL16 was found to exhibit scavenger receptor activity.29 In vitro CXCL16+ macrophages display a reduction in the uptake of oxLDL. Surprisingly, in vivo the deficiency of CXCL16 accelerates atherosclerosis with a marked increase of lesional macrophage content suggesting that CXCL16 is atheroprotective.40 Later it was described that CXCL16 increases the rate of cholesterol efflux to high-density lipoprotein and apoAI acceptor implying that CXCL16 is involved in macrophage reverse cholesterol transport by upregulating the 2 key cholesterol transporters ABCA1 and ABCG1,41 thus providing an explanation for the phenotype observed in Cxcl16−/− mice. Of note, deficiency for Cxcr6, the receptor for CXCL16, has been shown to be atheroprotective in late-stage atherosclerosis. However, the altered monocyte/macrophage content within the arterial wall resulted from a reduced influx of CD3+ effector T cells and an overall less inflammatory environment.42 More recently, it was described that CXCL5 via CXCR2 plays a protective role in atherosclerosis by limiting the cholesterol content of macrophages and foam cell formation, an effect mediated by increased ABCA1 expression.43 Interestingly, CXCL4, which is mainly produced by platelets, increases the expression of ABCG1 in macrophages.44 Albeit, the receptor for CXCL4 on macrophages is still unknown, previous work showed that CXCL4 also binds to oxLDL particles and enhances their uptake by macrophages.45 Although some contradictory findings demonstrate the complex roles of chemokines on macrophages and foam cell formation, these studies clearly highlight chemokines to directly affect foam cells formation and might be considered as future therapeutic targets.

More recently, it has been described that especially in established atherosclerosis, lesional macrophages proliferate locally and contribute to the plaque progression* pointing toward the importance of macrophage survival and continuous proliferation. Although MCSF (macrophage colony-stimulating factor) has
been appreciated to be the most important survival factor for macrophages within the vessel wall, another study demonstrated that the CX3CL1/CXCR1 axis delivers an important survival signal for lesional macrophages. Specifically, substitution of CX3CL1 rescued monocytes from experimentally induced cell death.\(^5^7\)\(^,\)\(^5^8\) Taken together this might at least partially explain reduced lesion formation in mice deficient for CX3CR1 and highlight the importance of the CXCL1/CXCR1 axis in plaque regression.

Within the past decade, macrophage heterogeneity, plasticity, and polarization gained more attention in the context of atherosclerosis and has been summarized recently.\(^5^9\) Although most knowledge stems from in vitro–based assays and little is known about functional connections between chemokines, chemokine receptors, macrophage subsets, and the outcome on atherosclerosis, CXCL4 has been described to induce a unique macrophage transcriptome. This M4 macrophage phenotype is distinct from M1 (classically activated macrophage) and M2 (alternatively activated macrophage) phenotype, thus defining a new macrophage subset.\(^5^4\) M4 macrophages can be found within human atherosclerotic plaques and are characterized by the expression of metalloproteinase 7 and the calcium binding protein S100A8.\(^5^0\) Moreover, CXCL4-induced macrophages display a complete loss of atheroprotective CD163 expression,\(^5^1\) which might result in a severe reduction in phagocytic capacity of this macrophage subset. Hence, M4 macrophages are assumed to be proinflammatory and proatherogenic.

### Macrophage Egress From Atherosclerotic Lesions

With chemokines being potent chemoattractant molecules, it was logically proposed that they could participate in the egress of macrophages and foam cells from the plaques. In a surgical model of plaque regression, an important reduction in plaque size because of emigration of foam cells from the atherosclerotic lesions to the lymphatic vessels was observed. This effect was abolished when both ligands for CCR7 (CCL19 and CCL21) were blocked.\(^5^2\) However, in this surgical model, spontaneous reanastomosis between lymphatic vessels and adventitia occur and may hence lead to false-positive results. Independent of that critical issue, statin treatment reduces macrophage cholesterol content and enhances CCR7 expression, which might depend on the presence of a sterile response element in the mouse and human CCR7 gene.\(^5^3\) Furthermore, the neuronal guidance molecule netrin-1, which inhibits the chemotactic responses of macrophages to various chemokines in vitro, may block macrophage chemotaxis to CCL19 or CCL21,\(^5^4\) thus diminishing potential CCR7-dependent macrophage egress from the plaque. In line, lethally irradiated Ldlr\(^{-/-}\) mice reconstituted with netrin-1–deficient bone marrow displayed increased macrophage emigration from the plaque.\(^5^4\) Interestingly, concentrations of netrin-1 and another neuronal guidance molecule semaphorin 3E decrease, whereas CCR7 expression is induced in regressing plaques.\(^5^4\)\(^,\)\(^5^5\) In a noninvasive model of plaque regression where the cholesterol levels are lowered via the re-expression of ApoE using an adenovirus in Apoe\(^{-/-}\) mice, no difference in plaque size and macrophage content could be observed between Ccr7\(^{-/-}\)Apoe\(^{-/-}\) and Apoe\(^{-/-}\) mice.\(^5^6\) This last finding suggests that macrophage emigration may not be an essential mechanism for plaque regression and other mechanisms controlling macrophage/foam cell fate might be dominant.

### Perspective

The importance of chemokines in the context of atherosclerosis was subject to plenty of studies within the past decades. However, clinical trials with either chemokine receptor or chemokine antagonists were disappointing. Reasons for such failures include prominent off-target effects because of cross-reactivity with receptors of similar structure, discrepancies between animal models and human diseases, and the importance of the targeted molecule in host defense and consequently compromised immune responses. In addition, the striking redundancy of chemokines in control of immune cell homeostasis, recruitment, and activation may render interference with just 1 molecule insufficient. Recent work has shown that delivery of annexin A1 fragments may override the redundant signals exerted by chemokines in the context of arterial monocyte recruitment.\(^5^7\) Despite such positive findings, to successfully target chemokines and chemokine receptors in future therapeutic studies, we need to better understand how chemokines shape monocyte function at steady state and during acute and chronic inflammation.

### Sources of Funding

This work is supported by the DFG (SO876/3-1, SO876/6-1, SFB914 TP B8, SFB1123 TP A6 and B5), the Else Krön er Fresenius Stiftung, the NWO (Nederlandse Organisatie voor Wetenschappelijk Onderzoek; VIDI project 91712303), and the LMUexcellence initiative.

### Disclosures

None

### References


30. May 2015

Significance

Atherosclerosis is a chronic inflammatory disease of the arterial wall. With its major clinical complications, such as stroke or myocardial infarction, atherosclerosis is still the leading cause for morbidity and mortality in Western societies. To successfully identify future therapeutic targets, in-depth understanding of underlying mechanisms and cellular key players is needed. Monocytes and their descendants are the most abundant leukocytes in the arterial vessel wall. Their entry into the atherosclerotic lesion, as well as their survival, activity, and egress, is critically shaped by chemotactic cytokine, that is, chemokines. This review highlights latest advances in the interplay between chemokines and monocytes with regard to the aforementioned processes.
Chemokines Control Mobilization, Recruitment, and Fate of Monocytes in Atherosclerosis
Maik Drechsler, Johan Duchene and Oliver Soehnlein

*Arterioscler Thromb Vasc Biol.* 2015;35:1050-1055; originally published online March 19, 2015;
doi: 10.1161/ATVBAHA.114.304649

*Arteriosclerosis, Thrombosis, and Vascular Biology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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