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Monocytes and macrophages in atherogenesis

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Abstract

Purpose of review—Monocytes and macrophages are key players in the pathogenesis of atherosclerosis and dictate atherogenesis growth and stability. The heterogeneous nature of myeloid cells concerning their metabolic and phenotypic function is increasingly appreciated. This review summarizes the recent monocyte and macrophage literature and highlights how differing subsets contribute to atherogenesis.

Recent findings—Monocytes are short-lived cells generated in the bone marrow and released to circulation where they can produce inflammatory cytokines and, importantly, differentiate into long-lived macrophages. In the context of cardiovascular disease, a myriad of subtypes, exist with each differentially contributing to plaque development. Herein we describe recent novel characterizations of monocyte and macrophage subtypes and summarize the recent literature on mediators of myelopoiesis.

Summary—An increased understanding of monocyte and macrophage phenotype and their molecular regulators is likely to translate to the development of new therapeutic targets to either stem the growth of existing plaques or promote plaque stabilization.

Keywords

atherosclerosis; macrophage; monocyte

INTRODUCTION

Atherosclerosis is the pathological consequence of the abnormal accumulation of cholesterol and triglyceride-rich apolipoprotein B lipoproteins within the intima layer of arterial walls. Monocytes and macrophages are components of the mononuclear phagocytic arm of the innate immune system and key players in atherogenesis. An initiating factor in the development of atherogenesis is the entry of monocytes into the subendothelium and their subsequent differentiation into macrophages [1,2]. Circulating leukocytes are strong predictors of atherogenesis and cardiovascular disease (CVD), and monocyte counts an

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independent risk factor for CVD progression and severity [3–12]. Recent technological and computational advances have increased our understanding of the heterogeneous nature of both circulating monocytes and macrophages in the setting of CVD. A detailed understanding of the subsets that promote or suppress plaque inflammation is anticipated to aid in the development of therapeutic options to reduce CVD progression. Within this review, we summarize recent literature relevant to monocyte and macrophage biology in the context of atherosclerosis.

MONOCYTE SUBTYPES

Monocytes are short-lived cells generated in the bone marrow and released to circulation where they can produce inflammatory cytokines and, importantly, differentiate into long-lived macrophages. Classically, hematopoietic ontogeny is described as a hierarchical system originating with hematopoietic stem cells (HSCs), which differentiate into myeloid, lymphoid, and erythroid-megakaryocytic lineages. HSC commitment towards the monocytic lineage involves the progressive differentiation of the common myeloid progenitor, to granulocyte-macrophage progenitor, to monocyte-dendritic progenitor, and finally to the common monocyte progenitor. Once considered a hierarchical process, recent data finds that hematopoiesis may be a dynamic process in constant flux [13]. A concept supported by the recent transcriptomic mapping of murine bone marrow, highlighting the plasticity and diversity of the cells in the bone marrow [14,15].

Human monocytes are classified according to the presence and relative abundance of two surface markers, the lipopolysaccharide (LPS) receptor, CD14, and the fragment crystallizable region gamma III receptor, CD16 [16]. Classical monocytes ($CD14^{++}CD16^{-}$) make up the majority of the monocyte pool, representing approximately 85%. Monocytes expressing both CD14 and CD16 are more mature, as they also express other surface markers typically present in tissue macrophages [17]. Intermediate monocytes, express abundant levels of both markers ($CD14^{+}CD16^{+}$) and account for approximately 5% of total monocytes, and nonclassical monocytes ($CD14^{+}CD16^{++}$) make up around 10%. Frequencies of all circulating human monocyte subsets are linked to various stages of CVD [18–25].

Recently, multicolor flow cytometry and mass cytometry analysis has further discriminated monocyte subtypes [26]. Hamers *et al.* recently described eight human monocyte subtypes distinguished by 34 unique surface markers. They define four subtypes belonging to the classical monocyte pool, one to the intermediate, and belonging to the nonclassical monocyte population [27■]. Further, they found the expansion of $Slan^{+}CXCR6^{+}$ nonclassical monocytes in individuals with coronary artery disease (CAD), and counts of this subset to positively correlate with CAD severity [27■]. This work, and others [28,29], unveils the phenotypic complexity of monocytes and highlights how different subtypes have a unique migratory and efferocytotic capacity, which may ultimately influence CVD.

Murine monocytes are divided into two subsets based on the expression of the lymphocyte antigen six complex (Ly6C). $Ly6C^{hi}$ monocytes express high levels of the C–C motif chemokine receptor 2 (CCR2) and do not express CX3C chemokine receptor 1 (CX3CR1), $CCR2^{+}CX3CR1^{-}Ly6C^{hi}$ ($Ly6C^{hi}$ monocytes). Classically, $Ly6C^{hi}$ monocytes are

proinflammatory and equivalent to the human classical ($CD14^{++}CD16^{-}$) and intermediate ($CD14^{+}CD16^{+}$) subsets. $Ly6C^{hi}CCR2^{+}$ are the precursor of the majority of monocyte-derived tissue macrophages, migrating to sites of injury and subsequently differentiating to inflammatory macrophages. Monocytes expressing the opposite expression pattern $CCR2^{-}CX3CR1^{+}Ly6C^{lo}$ ($Ly6C^{lo}$ monocytes) are designated as 'alternative' or 'patrolling' monocytes, and the counterpart of nonclassical ($CD14^{+}CD16^{++}$) monocytes [30,31].

Similar to their human counterparts, there is a growing appreciation of the heterogeneous nature of murine monocytes. Menezes *et al.* [32] recently profiled the heterogeneous nature of $Ly6C^{hi}$ monocytes and their capacity to differentiate to macrophages or monocyte-derived dendritic cells (moDCs). They established that PU.1 expression, a transcription factor involved in the differentiation of macrophages, is a crucial determinant in monocyte differentiation to inflammatory $iNOS^{+}$ macrophages or moDCs.

MONOCYTES AND ATHEROSCLEROSIS

Monocytosis, or the production of monocytes, is an established risk factor for the development of CVD [4,12,33–35]. Monocytosis is predictive of inflammation and cardiovascular risk factors, including hyperlipidemia, chronic stress, insufficient sleep, hypertension, and diabetes [36,37,38■■,39]. Increases in monocyte count predominantly refer to increases in proinflammatory monocytes, a phenotype which has a higher capacity to enter tissues and become macrophages. For example, classical monocytes isolated from obese individuals have a more significant proinflammatory potential as characterized by increased expression CCR2, a receptor essential for monocyte recruitment to tissues as occurs during the progression of atherosclerosis, or during HIV-mediated neuroinflammation [40,41].

FACTORS THAT PROMOTE MONOCYTOSIS

Impaired cholesterol efflux

Seminal preclinical studies linking myelopoiesis to CVD identified hypercholesterolemia as a significant contributing factor [34]. In addition to atherogenic effects on the arterial wall, hypercholesterolemia acts at the level of the bone marrow and spleen to enhance myelopoiesis, subsequently increasing the presence of circulating proinflammatory monocytes and accelerating macrophage accumulation in the artery wall [12]. Deficiencies in the cholesterol transporters ATP binding cassette (ABC) A1 and ABCG1 accelerate monocytosis by impairing hematopoietic stem and progenitor cells cholesterol efflux [34]. Cholesterol accumulation in lipid rafts on the membrane of HSCs leads to increased expression of the β subunit of the IL-3/granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor and enhanced proliferative responses to IL-3 and GM-CSF [34]. Others and we have shown that providing cholesterol acceptors (e.g., HDL, apoA-I) can suppress hypercholesterolemia-mediated myelopoiesis [12,33,42,43]. Recently, the connection between cholesterol handling and monocytosis was revisited in zebrafish. Gu *et al.* [44■■] found in both zebrafish with impaired cholesterol efflux capacity, and hypercholesterolemic individuals a master regulator of cholesterol metabolism, sterol regulatory element-binding

protein 2 (SREBP2), is significantly increased. SREBP2, a regulator of Notch signaling, favors the expansion of HSC, overall promoting myelopoiesis.

In addition, hematopoietic deficiency of angiopoietin-like protein 4, was recently shown to enhance leukocytosis and atherosclerosis in part mediated by increased myelopoiesis [45]. Further, the deletion of Map3k8, a mitogen-activated protein kinase, in myeloid cells regulates monocytosis by modulating apoptosis in circulating monocytes and by upregulating the expression of key cytokine receptor markers such as CCR2, overall promoting the recruitment of monocytes to the atherosclerotic lesions [46].

Diabetes

Diabetes, both types 1 and 2, and obesity are associated with CVD, and in the majority of cases present monocytosis and increased number of circulating neutrophils (neutrophilia) [33,43,47,48]. Release of S100A8/A9 by circulating neutrophils or adipose tissue macrophages promotes bone marrow myelopoiesis clinically and in preclinical models of type 1 diabetes and obesity [12,49,50]. In addition, hyperglycemia-induced S100A8/A9 increased the production of reticulated platelets, enhancing platelet–leukocyte interactions, a risk factor for CVD [51].

Reduction of hyperglycemia by blocking renal glucose reabsorption with a sodium-glucose cotransporter 2 inhibitor reduces diabetes-driven myelopoiesis, and monocytosis [12]. In addition, recent work from our group has reported that increasing cholesterol efflux capacity of bone marrow monocyte progenitors and from macrophages in the plaque can revert the adverse effects of diabetes on myelopoiesis and stem atherosclerosis progression. We showed that the pharmacological stimulation of the cholesterol transporter ABCA1 in the bone marrow of diabetic mice by antagonism of miR-33, or by providing an excess of the HDL/apoA-I decreased myelopoiesis in the absence of glucose-lowering and may represent a novel targetable pathway to reduce CVD risk in diabetic populations [33,42].

Stress

Psychosocial stress is a crucial mediator of acute and chronic cardiac events [35,52,53]. In response to stress, adrenal secretion of catecholamines exerts a myriad of effects including vasoconstriction and increased blood pressure. Hematopoietic cells are also a target of these hormones, as they express adrenergic receptors, which allow these cells to ‘sense’ emotions such as fear. Myeloid progenitor cell secretion of the C-X-C Motif Chemokine Ligand 12, a monocyte retention factor, is downregulated during psychosocial stress and social defeat promoting myelopoiesis and atherogenesis [35,54]. Additional studies have also confirmed how stress mobilizes HSCs to establish persistent splenic myelopoiesis [55].

Recent work has also linked sleep disruption to myelopoiesis and atherogenesis [38■■]. Mice subjected to sleep fragmentation produce more $Ly6C^{hi}$ monocytes and develop larger atherosclerotic lesions. McAlpine *et al.* identified a neuro-immune axis as a regulator of myelopoiesis; they found that stress reduced the production of hypocretin, a neuropeptide that controls the production of CSF1, an essential regulator of monocyte production.

In contrast, thermoneutrality, exercise, and weight loss are reported to limit monocyte bone marrow egress, and stem plaque progression [56–58]. Lower environmental temperatures are reported to increase monocyte count in humans and provide mechanistic evidence as to why those who live in warmer climates are protected against CVD compared with those in colder climates [59]. However, this link remains to be established by others, given recent reports that moderate temperature is a risk factor for the development of CVD [60,61].

TRAINED IMMUNITY

Cytokines can provoke functional changes in monocytes and influence the cellular outcome of hematopoiesis. Inflammatory insults can result in increased numbers and an altered activation state of monocytes even weeks after pathogen clearance; a phenomenon termed ‘trained immunity’. For example, emergency hematopoiesis during infections can have long-lasting effects characterized by a shift in cell fate resulting in higher production of immune cells, including monocytes [62]. Recently the concept of persistent proinflammatory reprograming of monocytes and macrophages in response to atherogenic compounds (e.g., oxidized LDL) was shown [63–65]. The initial findings obtained in macrophages are now extended to bone-marrow hematopoiesis and ‘training’ with IL-1β and atherogenic diet [66■,67].

Relevant to human populations, the concept of trained immunity appears to be translatable with a recent study reporting that monocytes from patients with familial hypercholesterolemia have a trained immunity phenotype and that lipid lowering with statins does not revert this proinflammatory phenotype [68]. Collectively, these studies demonstrate that inflammation-induced hematopoiesis can result in trained immunity characterized by long-term epigenetic effects on HSCs to generate higher quantities of monocytes possessing increased proinflammatory functions.

MACROPHAGE HETEROGENEITY IN ATHEROSCLEROTIC PLAQUES

Upon infiltration to tissues, short-lived monocytes differentiate into macrophages. Latin for ‘big eaters,’ macrophages serve to patrol tissues and engulf pathogens or apoptotic cells in response to local inflammatory responses. A defining feature of macrophages is their plasticity, which allows them to produce a tailored response to local microenvironment stimuli to either promote or resolve inflammation [69–73]. The classical model of macrophage activation defines both proinflammatory and anti-inflammatory macrophages with distinct physiological roles and activators [69,74]. *In vitro*, M1 macrophages polarize in response to Toll-like receptor, IFN-γ signaling and the presence of pathogen-associated molecular complexes, LPS, and lipoproteins. Primarily glycolytic [75], M1 macrophages secrete proinflammatory factors including high levels of IL-1β, IL-6, and TNF-α and contribute to tissue destruction [72,76,77]. Consistent with their inflammatory phenotype, they express proinflammatory transcription factors including nuclear factor-κB and signal transducer and activator of transcription (STAT) 1. At the other end of the spectrum are M2 macrophages, a fatty acid (FA) oxidation dependent-phenotype with anti-inflammatory properties [78]. M2 macrophages are polarized in response to the cytokines IL-4 and IL-13 and secrete anti-inflammatory factors, such as the IL-1 receptor agonist, IL-10 and collagen.

M2 macrophages are characterized by their expression of CD163, mannose receptor 1, resistin like β (Retnlb) and high levels of arginase-1, at least in murine models [70].

In the context of plaques, macrophages adhering to both the classically activated and alternatively activated subsets are present in both human and mouse lesions [2,79–83]. Macrophages in plaques have a decreased ability to migrate, impairing inflammation resolution that promotes atherogenesis. Persistent inflammation drives macrophage apoptosis, and in the absence of effective efferocytosis, leads to the accumulation of debris and apoptotic cells, facilitating plaque necrotic core formation [84]. In human lesions, macrophages expressing proinflammatory markers are in rupture-prone, unstable regions, and cells representing M2 macrophages reside in stable plaque regions [85–90].

An increasing number of reports demonstrate that the M1/M2 classification system represents an oversimplification of macrophage heterogeneity and that macrophages within plaques exist on an activation continuum [81,86,91]. In the context of atherosclerosis, several alternative macrophage classifications are now described [81,92]. Additional macrophage subtypes include atherogenic Mox and M4 macrophages [50,51], and antiatherogenic Mhem macrophages [45–47]. Recent technological advances in mass cytometry time of flight and single-cell RNA sequencing (scRNAseq) have identified a new $TREM^{hi}$ macrophage subtype. Characterized by low expression of inflammatory cytokines, and enhanced lipid metabolism and cholesterol efflux functions [57–59,93■■]. In addition, both monocytes and macrophages are reported to undergo programmed cell death pathway termed ‘METosis’ [94■,95]; whether this process occurs in the context of atherogenesis remains to be established.

IMMUNOMETABOLISM IN M1 AND M2 MACROPHAGES

Macrophages are highly plastic and tailor their responses to the immediate environment, with metabolic pathways playing a significant role in immune cell function [96,97]. In-vitro studies demonstrate that macrophage function and metabolic moiety are interconnected, indicating that it is possible to manipulate the function of macrophages by targeting specific metabolic pathways. M1 macrophages rely on aerobic glycolysis to produce pyruvate, and the pentose-phosphate pathway to produce NADPH. This process is known by ‘glycolytic switch,’ which is facilitated by an increase in the glucose transporter-1 and inhibited by the chemical analog 2-deoxy-D-glucose (2-DG). M1 macrophages also show a defective mitochondrial tricarboxylic acid cycle (TCA) cycle, which triggers the accumulation of cytosolic lactate, and a decrease in oxidative phosphorylation (OXPHOS) and FA degradation [98]. Conversely, M2 macrophages have an increased TCA cycle activity and OXPHOS, which facilitates the degradation of cytoplasmic pyruvate in the mitochondria, and contributes to a high FA oxidation capacity to produce higher levels of ATP [99■■]. Although 2-DG also inhibits macrophage M2 polarization, indicating that glucose could be necessary for M2 phenotype, recent work showed that this observation is an offsite effect of 2-DG inhibiting OXPHOS, and therefore limiting the production of ATP, which in turn contributes to the efficient activation of IL-4 canonical signaling pathway [100■■].

Macrophages readily take up modified lipoproteins and lipid aggregates, slowly progressing into lipid-laden foam cells. These cells show a reduced migratory capacity, indicating that lipid accumulation and mobilization are a critical factor in monocyte and macrophage motility [101,102]. Macrophages accumulate intracellular lipid droplets, similar to adipocytes or hepatocytes, but differ in lipid and protein composition [103,104]. In macrophages, different processes, including phagocytosis and receptor-mediated uptake mediate lipid uptake. Once engulfed, lipid-containing vacuoles are typically hydrolyzed by the lysosome to generate free cholesterol and FAs, which are re-esterified in the endoplasmic reticulum to form cytosolic lipid droplets [105■]. Conversely, M2 macrophages are reported to take-up and accumulate more cholesteryl esters and triglyceride than those stimulated with IFN-γ (M1-like) or unstimulated (M0) [106,107], accompanied by increased expression of the FA and oxidized lipoprotein receptor, cluster of differentiation-36 [108]. The exact role of lipid accumulation to macrophage polarization is not clear, but it is possible that an enhanced lipid droplet accumulation would fuel mitochondrial FA oxidation in M2 macrophages, a process that could be pharmacologically targeted to switch between macrophage phenotypic state [109,110].

Intracellular lipid mobilization is a complex process that influences macrophage function. Lipid droplets are hydrolyzed in lysosomes by the action of different lipases, a process dependent, at least in part, on autophagy [111]. Upon triglyceride and cholesteryl ester hydrolysis, the resulting FAs are oxidized to produce ATP or to serve as precursor molecules of lipid mediators such as eicosanoids [112■]. However, the fate of intracellular cholesterol is limited to serve membrane constituent, but in most cases, cholesterol is removed via cholesterol efflux. Transport-mediated efflux is primarily performed by ABCA1 and ABCG1 and is considered essential for the suppression of sustained macrophage inflammation in atherogenesis [113]. Highlighted by a recent study demonstrating that ABC-mediated cholesterol efflux is essential to prevent the activation of the inflammasome, a multi-complex protein system involved in the release of proinflammatory cytokines, which would favor atherosclerosis development and systemic inflammation [114].

Overall, a better understanding of the role of macrophage energy metabolism and how substrate availability influences metabolic capacity and phenotype is warranted. Further research is necessary to understand if diversion from a glucose-dependent M1-like phenotype to a FA-dependent M2-like macrophage phenotype *in vivo* will alter atherogenesis development and plaque stability.

MACROPHAGE PHENOTYPIC SWITCHING DURING ATHEROSCLEROSIS REGRESSION

Macrophage phenotypic switching *in vitro* is achievable as evidenced by the profound metabolic changes between M1 and M2 macrophages; however, this process is not well established *in vivo*. This is clinically relevant, as macrophage phenotype can significantly influence disease state and atherosclerotic lesion vulnerability and stability. In the case of atherosclerosis, M1 macrophages are predominant during atherosclerosis progression, documented to exacerbate plaque and systemic inflammation, which contribute to plaque

rupture. M2-like macrophages are more common in early lesions and are found enriched in stable plaques, where they reduce inflammation, promote tissue repair, and lead to plaque stabilization [115–117]. These findings can be applied to human atherosclerotic lesions, where M1 macrophages are predominant in symptomatic, unstable plaques, while macrophages expressing M2 markers are present in stable regions [118].

Until recently, it was not clear whether macrophages changed their polarization status in response to lipid-lowering or other signals during regression, or if newly recruited monocytes were the source of M2 macrophages in remodeling plaques. Using a combination of different knockout mouse strains, a sophisticated aortic transplantation model, and scRNAseq, it was recently reported that proinflammatory Ly6C^{hi} monocytes are essential for atherosclerosis regression and plaque stabilization [119]. Rahman *et al.* [119] found that atherosclerosis regression was dependent on the recruitment of circulating Ly6C^{hi} monocyte and their STAT6-dependent polarization to M2-like macrophages. In addition, in a follow-up study using scRNAseq in combination with macrophage fate mapping, it was found that in progressing and regressing plaques, there is a self-renewing population of monocytes that could partially contribute to sustaining the macrophage pool found in these lesions, either becoming M1-like or M2-like macrophages depending on the lesion environmental cues [120].

CONCLUSION

Monocytes and macrophages are key players in the pathogenesis of atherosclerosis, with their abundance and phenotype predictive of CVD prevalence and severity. We propose that understanding the molecular mechanism that governs myelopoiesis and monocyte production, and what dictates the subsequent myeloid phenotype will be essential for the development of therapeutics to suppress atherogenesis. To this end, evolving research into identifying modulators of monocyte and macrophage metabolism, with the goal of enriching established plaques with proresolving, stabilizing macrophages represents a promising step forward for the field.

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KEY POINTS

- Monocytes and macrophages are essential cell types in the development of atherosclerosis.
- Recent technological advances highlight the heterogeneous nature of both circulating monocytes and those found in atherosclerotic plaques and have facilitated the identification of new subsets.
- There is an increasing appreciation of how metabolism affects myeloid phenotype and function.
- An increased understanding of monocyte and macrophage phenotype and their molecular regulators is likely to translate to the development of new therapeutic targets to reduce cardiovascular disease risk.