

Macrophages

Ziad Mallat

Thanks to major advances in cellular and molecular biology, our understanding of the origins, heterogeneity, and functions of monocytes and macrophages, both in health and disease, is evolving at a considerable pace. Only during the past 2 years, new monocyte and dendritic cell subsets have been identified^{1–3}; essential transcriptional and epigenetic regulators of monocyte⁴ and tissue macrophage specification and maintenance⁵ have been uncovered; and an old concept of phenotypic transition of vascular smooth muscle cells (SMCs) to phagocytic macrophage-like cells has gained better understanding at the molecular level.^{6,7} The diverse roles of monocytes and macrophages in cardiovascular diseases have been highlighted in several interesting reviews published in *ATVB*, which addressed their origins, fates, and regulation^{8–10} in diverse settings such as atherosclerosis and associated cardiometabolic disorders,^{11–15} aortic aneurysm,¹⁶ and postschemic myocardial injury.¹⁷ Here, I summarize recent original work in those areas published in *ATVB* during the past 2 years.

Monocytes/Macrophages in Atherosclerosis

Monocytes/macrophages contribute to atherosclerosis through their diverse roles in cholesterol metabolism and the regulation of innate immune responses.

Lipid Handling

Several recent studies extended our understanding of the role of miR-33 in macrophages. miR-33 controls M2 polarization through the alteration of mitochondrial function¹⁸ and key metabolic (AMP-activated protein kinase)¹⁹ and autophagy effectors,^{20,21} of high relevance to atherosclerosis and associated cardiometabolic diseases. Long-term inhibition of miR-33 (subcutaneous anti-miR) in C57/Bl6 mice fed a high-fat diet upregulates hepatic ABCA1 (but not SREBP1), promotes whole-body oxidative metabolism and M2 polarization in adipose tissue, and decreases circulating triglyceride levels, although it does not improve insulin resistance.²² The results are reassuring given previous reports of undesirable effects in *mir33*^{-/-} mice or using other regimens of anti-miR-33 treatment.^{23–25} Additional work from the Moore laboratory shows that miR-33 targets the endolysosome and endoplasmic reticulum-associated oxysterol-binding protein-like 6 (OSBPL6), which leads to alteration of

intracellular cholesterol trafficking through abnormal endosome clustering, accumulation of free cholesterol, and reduction of cholesterol esterification.²⁶ Interestingly, miR-33 targeting of OSBPL6 is conserved in mice and nonhuman primates, and hepatic expression of OSBPL6 is positively correlated with circulating high-density lipoprotein cholesterol levels in humans,²⁶ further supporting the potential benefit of miR-33-targeted therapies in patients with cardiometabolic disease. A major in vivo target of miR-33 is ABCA1. Reduced expression of ABCA1 in humans is associated with a proinflammatory phenotype in macrophages, high levels of circulating proinflammatory cytokines, and increased statin-responsive vascular inflammation as revealed by ¹⁸FDG-PET/CT (¹⁸fluorine-2-fluoro-2-deoxy-D-glucose-positron emission tomography/computerized tomography) scanning in the carotid arteries.²⁷ ABCA1 is also an important direct target of miR-302a, and long-term in vivo treatment with anti-miR-302a in *Ldlr*^{-/-} mice significantly upregulates liver and aortic ABCA1 (ATP-binding cassette sub-family A1), increases circulating levels of high-density lipoprotein cholesterol, and reduces atherosclerotic plaque size and inflammation.²⁸ Furthermore, cholesterol homeostasis in macrophages is regulated by a newly identified pathway that associates upregulation of the long noncoding RNA RP5-833A20.1 to the induction of miR-382-5p. The latter targets the transcription factor NFIA, leading to downregulation of ABCA1 and ABCG1 expression and upregulation of SRA1, CD36, and NF-κB, with important consequences on plaque development and inflammation in *ApoE*^{-/-} mice.²⁹ Lipid metabolism is also controlled by LXRs. Recent data show that LXRβ binds to cell surface ABCA1 and inhibits its ubiquitination and lysosomal degradation. This process is dysfunctional in the hypercholesterolemic state because of increased binding of LXRβ to oxysterols and its dissociation from cell surface ABCA1.³⁰ LXR activation also promotes SREBP1-dependent polyunsaturated fatty acid (PUFA) synthesis in macrophages,³¹ which is in agreement with the finding that NCoR deletion in macrophages derepresses several enzymes involved in PUFA synthesis in an LXR-dependent manner.³² This phenotype of increased PUFA synthesis was also observed in atherosclerotic plaques of *ApoE*^{-/-} mice in vivo after treatment with an LXR agonist and was associated with reduced expression of proinflammatory genes, *Cox2* and *Il1b*.³¹ However, an important side effect of LXR activation in vivo is the induction of LXR-dependent hypertriglyceridemia. Interestingly, the latter can be prevented by concomitant treatment with an MEK1/2 inhibitor, which acts at least partly through inhibition of lipogenesis and activation of fatty acid oxidation.³³ Additional approaches to modulate the LXR pathway are explored. Vitamin D was recently shown to induce JNK1/2-dependent expression of CYP27A1, which resulted in increased production of 27-hydroxycholesterol, LXR activation, and led to ABCA1 (and ABCG1)-dependent stimulation of cholesterol efflux and attenuation of macrophage inflammation. Vitamin D deficiency in a

From the Department of Medicine, Division of Cardiovascular Medicine, University of Cambridge, United Kingdom; and Institut National de la Santé et de la Recherche Médicale, Paris, France.

Correspondence to Ziad Mallat, MD, PhD, University of Cambridge, Cardiovascular Medicine, Addenbrooke's Hospital, Hills Rd, Cambridge CB20SZ, United Kingdom. E-mail zm255@medschl.cam.ac.uk

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hypercholesterolemic swine model was associated with reduced plasma high-density lipoprotein cholesterol levels and increased cholesterol accumulation in lesions leading to acceleration of atherosclerosis, whereas vitamin D supplementation promoted an aposite phenotype.³⁴ Loss of mitochondrial CYP27A1 activity under conditions of oxidative stress and increased cholesterol hydroperoxides may substantially alter LXR-dependent cholesterol efflux by macrophages.³⁵ Additional unexpected pathways in macrophage cholesterol homeostasis and foam cell formation are being uncovered, such as Orai1-mediated calcium entry leading to ASK1-JNK/p38/calcineurin-dependent upregulation of SR-A,³⁶ or CD43-mediated control of cholesterol efflux,³⁷ although the precise mechanisms of the latter observation remain unexplored.

Innate Immune Functions

Plaque macrophages and macrophage-like cells may have different origins, including tissue-resident intimal antigen-presenting cells³⁸ and adventitial macrophages,³⁹ as well as transdifferentiated SMCs.⁶ Nevertheless, most plaque macrophages derive from circulating monocytes. The latter are recruited to the vessel wall after injury, differentiate into several phenotypes of macrophages and foam cells, proliferate in situ, and undergo various forms of cell death. They may even emigrate from the lesion under favorable conditions.

Regulation of monocyte/macrophage motility and migration affects their trafficking and accumulation within the lesions. Recent data indicate that extracellular ATP is released in response to arterial damage, induces endothelial activation and VCAM-1 expression through purinergic P2Y2 receptors, and promotes monocyte recruitment in the developing atherosclerotic lesion.⁴⁰ Defined chemokine/chemokine receptor pathways control the recruitment of selective monocyte subsets. FHL2 (four and a half LIM domain protein-2) is shown to interfere with this process, leading to selective recruitment of Ly6C^{hi} monocytes, in part through altered expression of CX3CL1 on endothelial cells, and CX3CR1 on monocytes.⁴¹ Part of this phenotype may be related to FHL2-mediated repression of NR4A1.⁴² Abnormal migratory behavior of plaque macrophages may impact the resolution of inflammation. Interaction of macrophages with the matrix plays an important role in this process. Periostin expression in macrophages enhances their migratory potential toward transforming growth factor- β and promotes their inflammatory phenotype,⁴³ whereas syndecan-1 expression is specific to differentiated M2 macrophages, increases their intrinsic motility, and limits their accumulation in atherosclerotic lesions,⁴⁴ possibly through enhanced clearance. Persistent vascular inflammation and macrophage accumulation in advanced lesions may involve additional pathways, such as the coagulation factor XI.⁴⁵

Macrophage activation substantially impacts the development and progression of atherosclerosis. NLRP3 inflammasome pathway is an important player, although most of the impact seems to occur at the early disease stages. Rajamaki et al⁴⁶ showed that p38 δ MAPK activates NLRP3 inflammasome by acting as a sensor of intracellular stress signals (potassium efflux, lysosomal leakage, and ROS formation), downstream of ATP, and cholesterol crystal stimulation. Given the concomitant upregulation of p38 δ MAPK and NLRP3 inflammasome

components in human coronary atherosclerotic arteries, this pathway may be worth of further investigation.

The HIF1 α (hypoxia-inducible factor alpha) pathway couples macrophage metabolism to innate immune activation. HIF1 α expression is upregulated in macrophages and CD11c⁺ cells of hypoxic plaque areas.^{47,48} Hypoxia promotes glucose uptake by macrophages and potentiates glycolysis in parallel with the development of a proinflammatory M1 phenotype (essentially increased NOS2), dependent on HIF1 α expression and 6-phosphofructo-2-kinase.^{47,49} Deletion of HIF1 α in murine myeloid cells (granulocytes and macrophages) does not affect the development of early atherosclerotic lesions⁴⁸ but significantly limits the accumulation of M1-like macrophages and reduces the development of advanced atherosclerosis.⁴⁷ This contrasts with the role of HIF1 α in CD11c⁺ antigen-presenting cells where it seems to limit proatherogenic Th1 cells through STAT3-dependent inhibition of interleukin-12 (IL-12) production.⁴⁸ In another study, inhibition of HIF-inducible prolyl 4-hydroxylase-2 in HIF-P4H-2-hypomorphic/C699Y-*Ldlr*^{-/-} mice or using an oral small molecule inhibitor induced a stabilization of HIF1 α and HIF2 α and led to a reduction of atherosclerosis. The atheroprotective effect was associated with reduced accumulation of white adipose tissue macrophages and improved serum lipid and metabolic profiles.⁵⁰

Two studies highlighted the role of serum- and glucocorticoid-inducible kinase-1 in macrophage biology. Myeloid deficiency in mineralocorticoid receptor attenuated vascular inflammation in a model of femoral artery injury and led to reduced macrophage migration, proliferation, and activation, in association with reduced activation of AP1/NF- κ B pathways.⁵¹ The results are consistent with the atheroprotective phenotype of serum- and glucocorticoid-inducible kinase-1 deficiency in *ApoE*^{-/-} mice, which was also attributed to reduced NF- κ B activation in macrophages.⁵² NF- κ B signaling is generally considered as proatherogenic, although its activation in macrophages may lead to atheroprotection in some settings.⁵³ In an intriguing study, NF- κ B activation in resident peritoneal macrophages, which is controlled by an S1P2/ $G_{\alpha_{12/13}}$ signaling pathway, promoted B1a cell expansion and activation, which led to increased production of natural IgM antibodies against oxidation-specific epitopes and protection against atherosclerosis.⁵⁴ The results suggest an interesting strategy of local targeting of peritoneal macrophages to limit atherosclerosis.

Damage-associated molecular patterns are potent activators of innate immune responses and contribute to atherosclerosis and vascular remodeling after injury. HMGB1 (high mobility group box 1) promotes intimal hyperplasia and vascular remodeling in a murine model of carotid artery wire injury. The effects are recapitulated in mice with TLR4 deficiency in myeloid cells, and after concomitant deletion and blockade of MyD88 and TRIF signaling.⁵⁵ Disulfide HMGB1 promotes cytokine and chemokine release by macrophages in a TLR4-dependent manner, and a specific inhibitor of HMGB1/MD2/TLR4 interaction reduces intimal hyperplasia in vivo.⁵⁵ Cellular fibronectin containing extra domain A (EDA) is another damage-associated molecular pattern absent from healthy arteries but highly expressed in atherosclerotic plaques, and its deletion reduces atherosclerosis. EDA

activates TLR4 in vitro⁵⁶ and in vivo.⁵⁷ In agreement with those data, EDA is now shown to activate macrophages and promote atherosclerosis in a TLR4-dependent manner.⁵⁸ Interestingly, TLR4 deficiency was unable to reduce atherosclerosis in EDA-deficient mice, pointing to EDA as a prominent endogenous TLR4 ligand in the context of atherosclerosis.⁵⁸

Proliferation, apoptosis, and efferocytosis control plaque macrophage accumulation, and inflammation⁵⁹ and may alter the efficacy of anti-inflammatory therapy.⁶⁰ Data indicate that enhanced macrophage apoptosis limits the development of early atherosclerotic lesions, a stage with preserved efferocytosis. JNK1 mediates endoplasmic reticulum stress-induced macrophage apoptosis, and deletion or pharmacological inhibition of JNK1 promotes early lesion progression in *Ldlr*^{-/-} mice, possibly through enhanced macrophage survival.⁶¹ Manipulation of JNK2 had no effects on atherosclerosis.⁶¹ However, the results are in disagreement with previous studies, which reported a reduction of atherosclerosis in the absence of JNK2 (because of reduced SR-A expression and foam cell formation), but no impact of JNK1 in *ApoE*^{-/-} mice on mixed C57BL6/129SV background and subjected to a longer duration of HFD.⁶² In addition to stage-specific differences in atherosclerosis, genetic background may have differential impact on cholesterol homeostasis and macrophage inflammatory responses,⁶³ which may in part account for the discrepant findings. The same group reported that inhibition of IKK α (involved in alternative NF- κ B activation) or its deletion in macrophages limits cell survival, presumably through suppression of mTORC2-mediated AKT^{S473} phosphorylation, while enhancing macrophage inflammatory status. Moreover, deletion of IKK α in bone marrow-derived cells reduces early atherosclerosis in *Ldlr*^{-/-} mice,⁶⁴ further supporting a role for macrophage apoptosis in limiting the development of early lesions. However, IKK α deletion profoundly affects T- and B-cell development and functions, which may also account for the atheroprotective effect. It is also important to note that promotion of macrophage apoptosis is unlikely to limit lesion development in a setting of impaired efferocytosis. Blockade of TIM-4 (T-cell immunoglobulin and mucin domain-4) prevents the efferocytosis of phosphatidylserine-expressing apoptotic cells and accelerates early lesion development in *Ldlr*^{-/-} mice.⁶⁵ Similarly, deletion of miR-155 accelerates late-stage atherosclerosis through impaired efferocytosis, dependent on BCL6 and RhoA, whereas it promotes early lesion development through enhanced macrophage proliferation dependent on CSFR1.⁶⁶

There is continued interest in the mechanisms that regulate the switch to M1- versus M2-like phenotype and their impact on plaque inflammation and progression. STAT-dependent signaling is important in this process. In this regard, myeloid deletion of GSK3 α suppresses STAT1 phosphorylation in response to M1 activation through enhanced STAT3 phosphorylation and formation of STAT3:STAT1 heterodimers, whereas it promotes IL-4-dependent M2 phenotype through enhanced STAT6 phosphorylation.⁶⁷ The resulting phenotype is associated with an attenuation of atherosclerosis.⁶⁷ Cathepsin C was suggested to alter M1/M2 phenotype in vitro. However, the mechanisms were unclear, and no changes of M1/M2 marker expression were detected in vivo in the absence of cathepsin C.⁶⁸ Heme uptake and degradation pathways are known to impact macrophage

phenotype in vitro and in vivo.⁶⁹ In further support of the importance of those pathways, hemopexin, a heme scavenger, attenuates heme-induced oxidative stress and induces a shift toward an M2-like phenotype with enhanced anti-inflammatory potential and improved ABCA1-dependent cholesterol efflux capacity.⁷⁰ Our understanding of the molecular mechanisms that control M1/M2 responses is also progressing. Lin et al⁷¹ developed new methodology to study those mechanisms in human macrophages. Their data revealed an important role for alternative splicing events, and more particularly splicing factor CELF1, in shaping gene expression of human monocyte-derived or iPS (inducible pluripotent stem cell)-derived macrophages in response to M1 stimulation.⁷¹ Interestingly, several cardiometabolic trait-associated variants occur within regulatory splicing factors that were differentially expressed in response to M1 activation, highlighting relevant novel targets.⁷¹

The interactions between SMC and macrophages and the potential for SMC transition to macrophage-like cells in atherosclerosis are receiving increasing attention. NG2 (neural/glia antigen 2) proteoglycan is shown to be important for very-low-density lipoprotein and low-density lipoprotein sequestration at the surface of synthetic SMCs, which then facilitate macrophage conversion to foam cells through direct cell-cell contact.⁷² Other studies indicate that cholesterol loading of SMCs converts them to inflammatory macrophage-like cells through downregulation of miR-143/145 and reduced myocardin expression.⁷ This may account, at least in part, for the acceleration of atherosclerosis in *ApoE*^{-/-} mice with hemizygous myocardin deficiency.⁷³ The resulting inflammatory microenvironment may also feedback to promote increased alteration of SMCs. Type I interferons, major players in atherosclerosis,⁷⁴ maintain SMC progenitors in an immature state,⁷⁵ suggesting that they might facilitate SMC transition to phagocytic macrophage-like cells.

Besides intimal and adventitial macrophages, perivascular adipose tissue-associated macrophages may contribute to the modulation of plaque inflammation and the response to injury. DOCA-salt-induced vascular injury polarizes fat-associated perivascular macrophages toward an M1-like phenotype through activation of C3/C5a, suggesting a role for the complement pathway in hypertension-associated vascular inflammation.⁷⁶ Epicardial/perivascular fat and their associated macrophages in human coronary atherosclerotic plaques express fatty acid-binding protein 4, which induces an inflammatory macrophage phenotype.⁷⁷ Maternal high-fat feeding promotes macrophage accumulation in periaortic adipose tissue, which enhances inflammation and accelerates plaque development in adult offspring.⁷⁸ Interestingly, recent data indicate that type 2 innate lymphoid cells critically control the phenotype and inflammatory status of periaortic fat-associated macrophages, with important consequences on the development of atherosclerosis.⁷⁹

Monocytes/Macrophages in Abdominal Aortic Aneurysm

The role of monocytes/macrophages in the pathophysiology of abdominal aortic aneurysm (AAA) and aortic dissection/rupture has been reviewed recently.⁸⁰ Most of AAA-associated macrophages originate from the circulating blood and seem to

be mobilized from the spleen in a B cell–dependent manner after angiotensin II stimulation.⁸¹ The activation and phenotype of AAA macrophages substantially determines the progression of AAA. Osteoclastic differentiation of macrophages is an important feature of AAA-associated macrophages and occurs in response to TNF/calcium phosphate stimulation in an NF- κ B/MAPK-dependent manner, but independently of RANK.⁸² Inhibition of osteoclastic differentiation by bisphosphonate limits CaCl₂-induced AAA.⁸² Oxidative stress is a major player in AAA and affects macrophage activation at various levels. ROS-induced activation of NLRP3 inflammasome promotes the development of angiotensin II–induced AAA,⁸³ and ROS-induced DNA damage has been implicated in macrophage activation and AAA progression after iron overload. Dietary iron restriction limits angiotensin II–induced AAA in mice.⁸⁴ In other studies, myeloid-restricted deficiency of membrane-bound thrombomodulin reduced angiotensin II–induced AAA formation, which was associated with reduced ROS formation and attenuated production of proinflammatory cytokines and MMP-9 by macrophages.⁸⁵ The mechanisms are still unexplored but could involve membrane-bound thrombomodulin interaction with TLR4/CD14 complex. PI3K δ is known to control signaling downstream of TLRs. Inactivation of PI3K δ in macrophages further makes them hyperresponsive to TNF signaling and increases AP-1 DNA binding activity downstream of TNF. This leads to enhanced macrophage activation and production of MMP-12 and increased susceptibility to CaCl₂-induced AAA.⁸⁶

Monocytes/macrophages also contribute to arterial inflammation and aneurysm formation in Kawasaki disease. In a mouse model of NOD1-induced coronary arteritis, NOD1 signaling in endothelial cells was required to induce the recruitment of Ly6C^{hi}-derived CD11c⁺ macrophages in a CCR2-dependent manner.⁸⁷ In another mouse model of lactobacillus casei cell wall extract–induced vasculitis, AAA developed in the infrarenal region similar to the human disease and was associated with the infiltration of CD11c⁺ macrophages.^{88,89} AAA in this model required MyD88 activation in hematopoietic cells,⁸⁸ with activation of NLRP3 in macrophages, leading to caspase-1–dependent IL-1 production and activation of (nonendothelial) stromal cells.⁸⁹ The disease was prevented by blockade of IL-1 α , IL-1 β , and IL-1R signaling, suggesting interesting therapeutic possibilities.⁸⁹

Conclusions

Monocytes/macrophages substantially shape the development, progression, and complications of cardiometabolic diseases. There is no doubt that recent technological advances in cellular and molecular biology, such as precise genetic editing and manipulation of human iPSC-derived macrophages,^{71,90} coupled with improved in vivo detection,⁹¹ tracking and manipulation^{92,93} of selective monocyte and macrophage subsets, will accelerate the translation of this increasing knowledge into effective therapeutic strategies.

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Disclosures

None.

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