Macrophage Phenotypes and Their Modulation in Atherosclerosis
Federica De Paoli; Bart Staels; Giulia Chinetti-Gbaguidi

Atherosclerosis is the result of a chronic inflammatory response in the arterial wall related to uptake of low-density lipoprotein by macrophages and their subsequent transformation in foam cells. Monocyte-derived macrophages are the principal mediators of tissue homeostasis and repair, response to pathogens and inflammation. However, macrophages are a homogeneous cell population presenting a continuum phenotypic spectrum with, at the extremes, the classically Th-1 polarized M1 and alternatively Th-2 polarized M2 macrophage phenotypes, which have been well described. Moreover, M2 macrophages also present several subtypes often termed M2a, b, c and d, each of them expressing specific markers and exhibiting specialized properties. Macrophage plasticity is mirrored also in the atherosclerotic lesions, where different stimuli can influence the phenotype giving rise to a complex system of subpopulations, such as Mox, Mhem, M(Hb) and M4 macrophages. An abundant literature has described the potential modulators of the reciprocal shifting between pro-inflammatory M1 and anti-inflammatory M2 macrophages including lesion stage and localization, miRNA, transcription factors such as PPARγ, KLF4 and NR4A family members, high-density lipoproteins and plaque lipid content, pathways such as the rapamycin-mTOR1 pathway, molecules such as thioredoxin-1, infection by helminths and irradiation. We hope to provide an overview of the macrophage phenotype complexity in cardiovascular diseases, particularly atherosclerosis. (Circ J 2014; 78: 1775–1781)

Key Words: Atherosclerosis; Macrophage phenotypes; Modulators

Macrophage Polarization and Plasticity
Bacterial products such as lipopolysaccharide (LPS) as well as inflammatory cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), prone macrophages to a classical activation (M1) state. Principal markers of M1 activation are interleukin-1β (IL-1β), TNF-α, IL-6, IL-12, IL-23, CXCL9, CXCL10 and CXCL11. These M1 macrophages are characterized by high production of nitric oxide (NO) and reactive oxygen intermediates, and participate in the resistance against intracellular parasites and tumor development. The M1-activated macrophages are named to mirror the fact that they are in the cascade of the Th1 polarized responses. Th2 cytokines are not simple inhibitors of this classical activation, but directly participate in the induction of a distinct macrophage phenotype: the alternative-activated M2 macrophage. M2 macrophages are mainly functional in tissue remodeling, angiogenesis and tumor progression; they are also involved in immunoregulation and allergic reactions. They are typically IL-10 high and IL-12 low.

To account for the complexity of macrophage phenotype, the M1/M2 spectrum needed to be extended. Thus, according to the stimulus they receive, alternative M2 macrophages can be classified into at least 4 distinct phenotypes. The M2a phenotype where “a” stands for “alternative”, is induced by IL-4 and IL-13 and M2 macrophages highly express the mannose receptor (MR/CD206), the decoy receptor IL-1RII and IL-1β receptor (IL-1R1) and...
receptor antagonist. M2b macrophages are induced by exposure to immune complexes and Toll-like receptor (TLR) agonists or IL-1 receptor ligands; they show the typical M2 characteristics, but also produce pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6. They are highly efferocytic, positive for CD68 and MR, and express pentraxin-3 and high amounts of TGF-α and TGF-β.

Moreover, growth factors such as granulocyte-macrophage colony stimulating factor (GM-CSF) or macrophage colony stimulating factor (M-CSF) lead to functional macrophage phenotypes similar to the M1 and M2 phenotypes.

The properties of alternative macrophages are well conserved among species, although the signature markers of alternative activation differ between murine and human macrophages. In particular, the transcription factor, found in inflammatory zone 1 (FIZZ1), the association of the chitinase 3-like 3 lectin (also referred as Yam1), arginase-1 (Arg1) as well as general arginine metabolism are specific for murine M2 macrophages.

Moreover, the M2d subtype does not express Yam1, FIZZ1 or MR. Finally, a new macrophage phenotype differing from the M1-M2 phenotype has been described and called M4 because it is induced by CXCL4 (formerly known as platelet factor 4).

**Table. Overview of the Different Macrophage Subpopulations Existing in Atherosclerotic Lesions**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Polarization signal</th>
<th>Markers and related genes</th>
<th>Cytokine/chemokine production, enzymes, other secreted factors</th>
<th>Functions and properties</th>
<th>Presence in atherosclerotic lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>IFNγ, LPS, TNFα</td>
<td>IL-1β, TNFα, IL-6, IL-12, IL-23, CXCL9, CXCL10, CXCL11, Arg-2 (M)</td>
<td>iNOS, ROI, IL-12(ih), IL-10(m), IL-23, IL-6, TNFα</td>
<td>Th1 immunological response, tumor resistance</td>
<td>M, H</td>
</tr>
<tr>
<td>M2a</td>
<td>Th-2 cytokines: IL-4 and IL-13</td>
<td>MR (H), IL1Ra (H), Arg-1 (M), FIZZ1 (M), Ym1/2 (M)</td>
<td>IL-10, TGFB, CCL22, CCL7</td>
<td>Tissue remodeling, efferocytosis</td>
<td>M, H</td>
</tr>
<tr>
<td>M2b</td>
<td>IC + LPS/IL-1β</td>
<td>IL-10(ih), IL-12(low)</td>
<td>IL-10(ih), IL-12(low), TNFα, IL-6</td>
<td>Immunoregulation</td>
<td>M, H</td>
</tr>
<tr>
<td>M2c</td>
<td>IL-10, TGFB, glucocorticoids</td>
<td>MR (H), Arg-1 (M)</td>
<td>IL-10, TGFB, PTX3</td>
<td>Mertk-dependent efferocytosis</td>
<td>M, H</td>
</tr>
<tr>
<td>M2d</td>
<td>TLR + Al agonists</td>
<td>TNFα(low), IL-12(low)</td>
<td>VEGF, IL-10, iNOS</td>
<td>Pro-angiogenic, tumor promotion</td>
<td>M</td>
</tr>
<tr>
<td>M4</td>
<td>CXCL4</td>
<td>MMP7, S100A8, MR</td>
<td>MMP12, IL-6, TNFα</td>
<td>Weakly phagocytic, minimal foam cell formation</td>
<td>H</td>
</tr>
<tr>
<td>Mox</td>
<td>oxLDL</td>
<td>HMOX-1, Srxm1, Txnrd1, Htf2</td>
<td>IL-10, IL-1β</td>
<td>Pro-atherogenic, weakly phagocytic</td>
<td>M</td>
</tr>
<tr>
<td>HA-mac</td>
<td>Hemoglobin/ haptoglobin</td>
<td>CD163(ih), HLA-DR(low)</td>
<td>HMOX-1</td>
<td>Anti-atherogenic, hemoglobin clearance</td>
<td>H</td>
</tr>
<tr>
<td>M(Hb)</td>
<td>Hemoglobin/ haptoglobin</td>
<td>CD163, MR</td>
<td>LXRα, ABCA1, ABCG1</td>
<td>Hemoglobin clearance, strong cholesterol efflux</td>
<td>H</td>
</tr>
<tr>
<td>Mhem</td>
<td>Heme</td>
<td>CD163, ATF1</td>
<td>LXRβ</td>
<td>Anti-atherogenic, erythropoietic</td>
<td>M, H</td>
</tr>
</tbody>
</table>

Arg, arginase; FIZZ1, found in inflammatory zone 1; H, human; HMOX, heme oxygenase; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; LXR, liver X receptor; M, murine; MerTK, Mer receptor kinase; MMP, matrix metalloproteinase; Nrf2, redox-regulated transcription factor 2; oxLDL, oxidized low-density lipoprotein; PTX3, pentraxin-3; ROI, reactive oxygen intermediates; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

**Macrophage Phenotypes in Atherosclerotic Lesions**

**Human Lesions**

Human atherosclerotic lesions have a highly heterogeneous phenotype and environment. Many factors in the microenvironment can modulate the macrophage phenotype: not only cytokines, but also bioactive lipids (cholesterol crystals, oxidized lipoproteins, fatty acids) and immune complexes. The presence of pro-inflammatory macrophages was demonstrated several decades ago, whereas the identification of alternative macrophages remained elusive for many years. More recently, M2 macrophages, positively stained for CD68 and MR, were first identified far from the lipid core, in more stable zones of the lesion. CD68<sup>MR</sup> macrophages are present in areas rich in IL-4 and are filled with less and smaller lipid droplets than CD68<sup>MR</sup> macrophages.

Boyle et al identified a novel macrophage subset located in hemorrhagic zones of plaques, called HA-mac, defined by high levels of CD163, but low levels of human leukocyte antigen-DR. These macrophages are mainly anti-atherogenic and involved in hemoglobin clearance and reduction of oxidative stress. Closely related to HA-mac are Mhem macrophages, with their high potential for ingesting erythrocytes, and displaying a strong heme-dependent phosphorylation and activation of the activating transcription factor 1. This transcription factor induces heme oxygenase (HMOX-1) expression and the liver X receptor α (LXRα)/ABCA1/apolipoprotein-E (ApoE) cascade that has a protective function against foam cell formation. However, hemoglobin/haptoglobin ingestion by macrophages gives rise to M(Hb) macrophages with high surface expression of the M2 markers MR and CD163. Neovascularization is frequently found in atherosclerotic plaques and leads to erythrocyte infiltration with a consequent accumula-
tion of iron in the lesion. CD68⁺ MR⁺ alternative macrophages strongly colocalize with iron deposits, further suggesting a role for these M2 macrophages in iron handling and recycling.³¹

An M4 macrophage population has been identified in human atherosclerotic plaques, based on the expression of the matrix metalloproteinase (MMP) 7 and the calcium-binding protein S100A8.³² M4 macrophages express MMP12, the MR but also some pro-inflammatory cytokines such as IL-6 and TNF-α. As a trade mark of CXCL4 polarization, M4 macrophages do not express the hemoglobin-haptoglobin scavenger receptor CD163.²³

**Murine Lesions**

Besides the M1, M2 and heme/hemoglobin-related macrophages that have been identified in both humans and mice, a distinct phenotype specific for mouse plaques is constituted by Mox macrophages.²⁴ Mox macrophages are induced by the accumulation of oxidized phospholipids in the lesions. This subpopulation highly expresses HMOX-1, by a mechanism involving the redox-regulated transcription factor 2.²⁵ FACS analysis performed on established aortic lesions from LDLR⁻/⁻ mice showed that M1 macrophages represent approximately 40%, with Mox 30% and M2 20% of the total number of macrophages.²⁶

Although the in vitro conditions to generate the different subtypes of macrophages are well defined, the in vivo situation is more complex. Several subpopulations of macrophages coexist simultaneously in atherosclerotic lesions and show specific characteristics according to the zone where they are located (Table). However, the mechanisms controlling the generation of the different subtypes, together with their specific functions, are poorly understood.

**Macrophage Phenotypes and the Progression of Atherosclerosis**

Given the complexity of the macrophage phenotypes and their ability to exert opposing pro- and anti-inflammatory properties, it is speculated that their phenotypic modulation plays a role in the development of atherosclerosis.

Macrophages infiltrating atherosclerotic lesions in young (20-week-old) ApoE knockout (KO) mice fed a chow diet show the alternative-Arg2⁺ M2 phenotype, while during disease progression, a switch from the M2 to the M1 phenotype is observed. Interestingly, the cytokine microenvironment changes over time: an increase in the expression of IFN-γ at the expense of IL-4 is observed in advanced atherosclerotic lesions, leading to enrichment with pro-inflammatory Arg2⁻ M1 macrophages during plaque growth.²⁸ Moreover ApoE KO mice fed a high-cholesterol diet show after 10 weeks high levels of M-CSF driven alternative-M2 marker expression (selenoprotein-1, stabilin-1 and CD163) that goes in parallel with plaque development. By the way, the GM-CSF-driven M1-related gene proplatelet basic protein (PPBP) is induced only in very early lesions (6 weeks of diet) and then its expression decreases. These findings mirror the in vivo GM-CSF:M-CSF ratio that changes during the progression of atherosclerotic lesions.²⁶

In humans, the content of both M1 and M2 macrophages increase during the progression of atherosclerotic lesions.²⁷ Moreover, both phenotypes are more abundant in unstable vs. stable plaques. Interestingly, the different macrophage subtypes are found in different locations in the plaque: M1 macrophages are mainly found in rupture-prone zones, such as the plaque shoulder, whereas there are no dominant phenotypes in the fibrous cap. Surprisingly, M2 macrophages strongly inflame the vascular adventitia.²⁷ More recently, analysis of the relationship between macrophage phenotype and plaque vulnerability by comparing specimens from symptomatic patients suffering from acute ischemic attack and asymptomatic patients without any symptoms, revealed that M1 macrophages are exclusively found in plaques of symptomatic patients and higher in unstable plaques, whereas M2 macrophages are present in both symptomatic and asymptomatic patients, being higher in stable plaques.²⁸

These observations led to the hypothesis that the M1/M2 macrophage ratio, as well as their specific location within the atherosclerotic lesion, can be a determinant of plaque stability.

**Modulation of the Macrophen Phenotypes**

Several factors have been found to modulate reciprocal skewing between the pro-inflammatory M1 and the anti-inflammatory M2 macrophage phenotypes.

**Modulation by MicroRNAs (miRNAs)**

miRNAs are short non-coding RNAs of approximately 22nt, which have been highly conserved during evolution.²⁹ Transcribed by RNA polymerase II as a primary mRNA, they are further processed by Drosophila and Dicer and subsequently loaded onto the RISC complex.³⁰ Once in mature form, they bind to target miRNAs, leading to their degradation and/or repression of translation.³¹ miRNAs play pivotal roles in the regulation of macrophage development and functions.³² Several miRNA are expressed in human and murine atherosclerotic plaques.³³,³⁴ Among the best studied miRNAs, miR-155 is highly expressed in macrophages, even though also expressed by a subset of smooth muscle cells in atherosclerotic lesions.³⁵ miR-155 is classified as a pro-inflammatory miRNA: its expression is induced by TLR stimulation and it enhances the production of pro-inflammatory cytokines. Moreover, miR-155 is upregulated in M1 macrophages, where it promotes the classical activation phenotype by increasing CCL2 and TNF-α production via inhibition of B-cell lymphoma-6 protein (BCL6) expression.³⁶ Deletion of miR-155 in hematopoietic cells reduces advanced atherosclerotic plaque formation.³⁷,³⁸ Moreover, miR-155 also contributes to the alteration of macrophage phenotype by reducing the expression of some M2 markers (Arg-1 and Chi3l3).³⁹

By contrast, miR-147, which is also induced by pro-inflammatory stimuli, constrains the inflammatory response of macrophages, being part of a negative feedback loop inhibiting the NFκB pathway.³⁹ Together with miR-147, miR-21 and the 2 members of the miR-146 family (miR-146a/b) are inhibitors of NFκB, reducing pro-inflammatory cytokine production and, concerning miR-21, increasing the expression of the anti-inflammatory cytokine IL-10.⁴⁰

Another 2 miRNAs have been identified as participating in the modulation of the macrophage phenotype: let-7e, which is induced by the LPS-activated-protein kinase Akt1 and represses TLR4 signaling,⁴¹ and miR125b, which is downregulated by Akt1 and targets the transcription factor IFN regulatory factor 4, thus inhibiting the alternative activation of macrophages.⁴²

**Modulation by Transcription Factors**

During the past few years, several studies have outlined the role of nuclear receptors and transcription factors in the modulation of the macrophage phenotype in atherosclerosis (Figure). One of the most important is peroxisome proliferator-activat-
ed receptor γ (PPARγ), the expression of which positively correlates with the expression of alternative M2 markers such as MR, AMAC and IL-10, in human carotid plaques. In vitro, PPARγ primes human alternative polarization only when it is activated at the initial stage of monocyte differentiation. In mice, PPARγ controls Arg1 expression in concert with PPARδ. By contrast, PPARα and PPARβ/δ activation do not modulate M2 marker expression in human macrophages. Different responses are elicited by PPARs in tissues not directly linked with atherosclerosis development. PPARβ/δ, for example, was shown to be necessary for the regulation of the alternative phenotype of murine Kupffer cells and adipose tissue macrophages. PPARγ affects the M1/M2 balance in obese mice by decreasing the number of M1 macrophages and inducing the expression of M2 markers in adipose tissue.

Kruppel-like factor (KLF) 4 is essential for alternative polarization in mice, by increasing the expression of Arg1 via the STAT6-signaling pathway and decreasing the expression of pro-inflammatory genes via partial inhibition of NF-κB transcriptional activity. More recently, KLF6 was also identified as a transcription factor playing a role in macrophage polarization both in humans and mice, inhibiting the M2 phenotype by suppressing PPARγ expression and promoting the M1 phenotype in concert with NFκB. However, no data are currently available to directly link these 2 members of the KLF family with atherosclerosis.

LXRα indirectly decreases the expression of the M2 marker Arg1 in murine macrophages, hence contributing to plaque regression. In human macrophages, LXRα is expressed at relatively low levels in IL-4 polarized CD68+MR+ macrophages, which show a decreased capacity to handle and efflux excess cholesterol. Recently, the expression of the nuclear receptor Rev-erbα was demonstrated in human carotid artery atherosclerotic lesions, colocalizing with the pan-macrophage marker CD68. Rev-erbα elicits anti-atherogenic functions by increasing the expression of several M2 markers (Arg1, MR and Ym1/2) and decreasing the mRNA level of the M1 marker, inducible macrophage-type NO synthase (iNOS).

Nuclear receptors of the NR4A family have also been highly investigated for their implication in macrophage polarization in mice, but data for human macrophages are still lacking. Nur77 (also referred to as NR4A1) is more highly expressed in LyC6C–CCR2–CXCR1hi CD62L– patrolling or resident monocytes that tend to differentiate into alternative M2 macrophages. Moreover, Nur77-deficiency in mice leads to a switch toward the pro-inflammatory M1 phenotype with a reduction in IL-12, iNOS and TNF-α expression combined with an increased Arg1 expression. However, these results were recently challenged by a study showing that neither Nur77 nor NOR1 (also known as NR4A3) are main players in macrophage polarization. Transplantation of Nur77- or NOR1-deficient hematopoietic precursors into LDL-R deficient recipient mice did not result in any changes toward the M1 phenotype.

Estrogens exert their biological functions by binding to es-
trogen receptor (ER) α (NR3A1; ERα) and β (NR3A2; ERβ). Hematopoietic/myeloid-specific deletion of ERα gives rise to more severe atherosclerotic lesions in mice. Expression of ERα is induced by IL-4 and is required for the induction of M2 markers such as PPARγ/β, Chil3, TGF-β, as well as the enzyme translaminatase 2 (TGM2), while the expression of pro-inflammatory markers IFN-γ, IL-6 and IL-1β is down-regulated.

Modulation by High-Density Lipoproteins (HDLs)
HDLs protect against atherosclerosis through a process called reverse cholesterol transport. In fact, HDLs are good acceptors of cholesterol derived from foam cells. HDLs also transfer cholesteryl esters to triglyceride-rich particles via cholesteryl ester transfer protein to form chylomicron remnants and low-density lipoprotein, which are then transported to tissues and catalyzed. Moreover, they have been shown to possess potent anti-inflammatory activities, such as preventing monocyte adhesion to the surface of cultured human umbilical vein endothelial cells.

Given these pleiotropic anti-atherogenic activities, several laboratories have investigated whether HDLs can affect macrophage alternative polarization. Feig et al demonstrated in a murine model of atherosclerosis regression that normalization of HDL content leads to a reduction in the CD68+ macrophage content of plaques, together with an increase in M2 markers (Arg1, CD163 and FIZZ1). HDL regulation of Arg-1 and FIZZ1 occurs through a STAT6-dependent mechanism. By contrast, HDLs do not induce any change in the expression of alternative polarization markers in human M2 macrophages.

Modulation by Thioredoxin-1 (Trx-1)
Trx-1 is a protein secreted by a variety of normal and transformed cells and can be detected in plasma. It plays a critical role in the protection against oxidative stresses. Trx-1 maintains intracellular cysteine residues in the reduced state, and acts upon release as a cytokine. Trx-1 also exerts anti-inflammatory and anti-apoptotic effects and recently its potential role as a modulator of the macrophage phenotype has been investigated. In vitro experiments showed that Trx-1 treatment promotes alternative M2 macrophage polarization by inducing the expression of MR and IL-10, and decreasing the production of M1 cytokines, such as TNF-α and MCP1. Consistently, in vivo experiments in transgenic human ApoE2 mice challenged with LPS and treated with Trx-1 showed a shift from the M1 to the M2 phenotype combined with a reduction in atherosclerotic lesions. Moreover, Trx-1 colocalizes with MR but not with TNF-α in human atherosclerotic plaques. By contrast, the truncated form of thioredoxin, Trx-80, which has pro-inflammatory and atherogenic properties, resulted in attenuation of the M2 phenotype and enhancement of atherosclerosis progression with macrophages exhibiting an M1 state.

Modulation by Rapamycin (RAPA) and mTOR Pathway
RAPA is a macrolide triene antibiotic produced by the actinomycete Streptomyces hygroscopicus, which is commonly used as an immunosuppressor. RAPA inhibits T-cell proliferation by targeting the mammalian/mechanistic target of RAPA (mTOR) phosphatidylinositol 3’-kinase-like family. mTOR has been demonstrated to be a critical regulator of monocyte, macrophage and myeloid dendritic cell survival and proliferation.

In vitro as well as in vivo, RAPA induces the cell death exclusively of M2 alternative macrophages and not M1 macrophages. Furthermore, it induces an imbalance between these 2 macrophage phenotypes by increasing the expression of classical activation (CCR7, IL-6, TNF-α, IL-1β) markers in M1 macrophages and by decreasing the expression of M2 markers (IL-10, MR, CCL18 and VEGF) in both M1 and M2 macrophages. In parallel, bone marrow-derived macrophages derived from mice with a constitutive activation of the mTOR complex (mTORC1) showed a strong defect in M2 marker expression and an exacerbated M1 response to LPS stimulation, because of mTORC1 alteration of Akt signaling independent of PPAR7 activation. Simultaneously, RAPA treatment rescues the expression of M2 markers. Globally, these data suggest that further investigations are needed to elucidate the role of RAPA and the mTOR pathway in macrophage polarization.

Modulation by Helminth Infection
A negative correlation between Schistosoma infection and the incidence of cardiovascular diseases has been reported in the past. Helminths are eukaryotic parasitic worms that induce a Th2 response and alternatively activated macrophages that are crucial for host survival. After S. mansoni infection, a higher hepatic expression of alternative macrophage markers (Ym1/2, FIZZ1 and Mgl2) is observed. The S. mansoni-derived soluble egg antigens (SEAs) have been reported as new modulators of the macrophage phenotype in vivo. Indeed, SEA treatment of LDLR–/– mice reduced plaque size, as shown by a reduction in lesion cholesterol content, but also to decreased expression of inflammatory markers (MCP1, VCAM1, TNF-α), damping IL-10 production.

Modulation by Irradiation
Cancer patients undergoing thoracic radiotherapy show an increased incidence of localized atherosclerosis. In fact, irradiation of early stage atherosclerotic plaques accelerates the severity of the lesions, inducing a strong inflammatory response and priming them for rupture. Because older cancer patients treated by thoracic irradiation often have early or advanced atherosclerosis, the effect of irradiation on macrophage polarization has been evaluated. Local 14-Gy irradiation of pre-existing aortic atherosclerotic lesions in ApoE–/– mice resulted in smaller lesions containing a higher amount of M1 and a decreased number of M2 macrophages. Besides, irradiation decreased the effector cytotoxic capacity of M2 macrophages, possibly contributing to the larger number of apoptotic cells in the lesions, creating a stronger inflammatory environment. This change in plaque cytokine content switches macrophages to the M1 phenotype, which could thus contribute to the increased M1/M2 macrophage ratio in irradiated lesions.

Conclusions
Monocyte-derived macrophages are the main actors in the development of atherosclerosis, and respond to a multitude of stimuli that modulate the phenotype of the macrophages, according to their capacity to skew reciprocally from the M1 to M2 phenotype. The natural purpose of this plasticity is the necessary adaptation to the lesion environment in an attempt to reach equilibrium between their destructive and/or reparative functions. It is crucial to define the markers, properties and localization for all the different subpopulations of macrophages in order to better define their relative roles. Moreover, the discovery of novel molecules/mechanisms able to modulate the macrophage phenotype will allow the identification of potential therapeutic targets and approaches to treat athero-
sclerosis and related disorders.

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References


