Macrophage complexity in human atherosclerosis

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Download date: 22 Oct. 2023
Macrophage complexity in human atherosclerosis: opportunities for treatment?

Erik A.L. Biessen\textsuperscript{a,c} and Kristiaan Wouters\textsuperscript{b}

Purpose of review
The pivotal role of macrophages in experimental atherosclerosis is firmly established, but their contribution to human disease is less well defined. In this review we have outlined the current insights on macrophage phenotypes and their presumed precursors, monocytes, in clinical atherosclerosis, and their association with disease progression. Moreover, we will assess major clinical modifiers of macrophage-mediated plaque inflammation and define the outstanding questions for further study.

Recent findings
Our survey indicates that macrophage accumulation and status in human plaques are linked with lesion progression and destabilization as well as with symptomatic coronary artery disease. Likewise, levels of their precursors, circulating monocytes were repeatedly seen to associate with atherosclerosis and to predict clinical outcome. Furthermore, the presence and phenotype of both macrophages and monocytes appears to be responsive to the traditional risk factors of atherosclerosis, including hypercholesterolemia, hypertension, and type 2 diabetes, and to treatment thereof, with clear repercussions on disease development.

Summary
Although plaque macrophages and their precursor cells do represent attractive targets for treating cardiovascular diseases, this therapeutic avenue requires much deeper understanding of the complexity of macrophage biology in human atherosclerosis than available at present.

Keywords
arteriosclerosis, innate immunity, macrophage, monocytes, polarization, rupture

INTRODUCTION
Ischemic heart diseases (IHDs) are a leading death cause worldwide [1], despite major advances in diagnosis and – mostly preventive – treatment of known risk factors, such as dyslipidemia, type 2 diabetes, hypertension, and hypercoagulation. Inflammation is increasingly viewed as a causal process in IHD pathophysiology, affecting atherosclerotic lesion progression and postischemic responses in heart, brain, or kidney tissue. Macrophages are recognized as key mediators in IHD and related inflammation, primarily owing to their abundant presence in human ruptured plaque and based on numerous experimental studies in mouse models of disease [2**].

Although the role of macrophages in preclinical models of disease has been amply documented, their direct contribution to human disease is much less developed. With recent major breakthroughs in our understanding of macrophage biology, heterogeneity, and function under homeostatic but also chronic inflammatory conditions, the evaluation of their relevance for and extrapolation of these findings to the clinical situation of human atherosclerosis is gradually emerging.

The present review aims to present an overview of the current insights on the presence and status of macrophages and their presumed precursors, monocytes, in clinical atherosclerosis, and their association with disease progression. Moreover, we will review the major clinical modifiers of macrophage-dependent plaque inflammation and will define the outstanding questions for further study.

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KEY POINTS

- Human plaque harbors a broad spectrum of macrophage phenotypes, at which M1 polarization seems to be associated with plaque progression and instability.
- Circulating intermediate monocyte numbers are linked to cardiovascular outcome.
- Therapies against known risk factors of atherosclerosis potentially impact plaque macrophage phenotype and activity.

Monocytes and macrophages in human atherosclerosis: current status

Apart from their role in infection macrophages exert many functions to maintain tissue homeostasis, like clearance of senescent erythrocytes or apoptotic cells [3]. Consequently, macrophages react upon different environmental cues. Exemplary of this capability is the oversimplified classification of macrophages into classically activated macrophages (M1) and immune-modulatory alternatively activated macrophages (M2) [4], representing extreme phenotypes of multiple activation states [3]. Apart from M1 and M2 macrophages, thought to be proatherogenic and atheroprotective respectively, other subtypes have been described, like M2a, M2b, M2c, and M2d (reviewed in [5]). In the context of atherosclerosis, different plaque-specific signals generate several macrophage phenotypes, at least in vitro, like Mhem macrophages activated by heme [6,7], Mhb macrophages stimulated by hemoglobin [8], M4 macrophages induced by CXCL4 [9], and Mox macrophages after treatment of murine macrophages with oxidized phospholipids [10] (reviewed in [11]). This empirical inflation-prone conception of macrophage polarization has recently been challenged by Xue et al. [12] proposing a new transcriptome-based model for macrophage phenotypic adaptation.

Until now, most efforts to define the macrophage phenotype in atherosclerosis have applied the M1/M2 classification scheme. Brand et al. [13] were the first to show prominent nuclear factor-kB (NF-κB) activity in human plaque macrophages, hinting to a M1 polarized phenotype. Vulnerable plaque morphology correlated with COX2+ (M1) and MMP14+ macrophage presence (foam cells), whereas it was inversely associated with CD206+ (M2) [14]. In slight contrast to this study, Stöger et al. failed to demonstrate a global predominance of M1 over M2 macrophages in vulnerable plaque. Nevertheless, M1 macrophage marker staining mainly confined to rupture-prone shoulder regions of the plaque, whereas M2 markers were present in vascular adventitial tissue [15]. This distribution relates M1 macrophages to worse cardiovascular prognosis. Table 1 provides an overview of studies linking human plaque macrophages with clinical outcome. Total plaque macrophage burden, defined by CD68-positive staining, associates with increased risk of stroke [16] and platelet reactivity [17], whereas associations with stenosis were less clear [18,19].

Table 1. Summary of studies linking human plaque macrophage phenotype with clinical outcome of cardiovascular diseases

<table>
<thead>
<tr>
<th>First author Year</th>
<th>Subset</th>
<th>Outcome</th>
<th>n</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hellings et al. 2008</td>
<td>CD68+ macrophages</td>
<td>Restenosis ↓</td>
<td>500</td>
<td>[19]</td>
</tr>
<tr>
<td>Hellings et al. 2010</td>
<td>CD68+ macrophages</td>
<td>CV events and stroke ↑</td>
<td>236</td>
<td>[22]</td>
</tr>
<tr>
<td>Scholtes et al. 2012</td>
<td>MMP-12 producing macrophages a</td>
<td>Fibrotic cap thickness ↓</td>
<td>20</td>
<td>[21]</td>
</tr>
<tr>
<td>Medbury et al. 2013</td>
<td>CD68+ós, CD64+, CD86+ cells (M1)</td>
<td>Fibrotic cap thickness ↓</td>
<td>20</td>
<td>[21]</td>
</tr>
<tr>
<td>Lee et al. 2013</td>
<td>CD68+cd11c+ macrophage content</td>
<td>In AMI</td>
<td>52 vs. 32</td>
<td>[23]</td>
</tr>
<tr>
<td>Cho et al. 2013</td>
<td>CD68+cd11c+ macrophage content</td>
<td>In AMI</td>
<td>52 vs. 34</td>
<td>[24]</td>
</tr>
<tr>
<td>Rutter et al. 2014</td>
<td>CD68+ macrophages</td>
<td>Platelet reactivity ↑</td>
<td>91</td>
<td>[17]</td>
</tr>
<tr>
<td>Howard et al. 2015</td>
<td>CD68+ macrophages</td>
<td>Stroke risk ↑</td>
<td>1640</td>
<td>[16]</td>
</tr>
<tr>
<td>Merckelbach et al. 2016</td>
<td>CD68+ macrophages</td>
<td>Stenosis</td>
<td>760</td>
<td>[18]</td>
</tr>
<tr>
<td>de Gaetano et al. 2016</td>
<td>M1 gene expression b</td>
<td>In symptomatic CAD</td>
<td>80</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>M2 gene expression c</td>
<td>In symptomatic CAD</td>
<td>80</td>
<td>[25]</td>
</tr>
</tbody>
</table>

aMMP12/CD68 ratio.
bTNF, IL6, IL8.
cCCL22, IL10, IL-13, CD163, CD2016.
Although total plaque macrophages did not predict vascular outcome in a study including 818 endarterectomy patients [20], further classification of macrophages based on M1 and M2 markers does show clinical relevance of macrophage burden in the plaque (Table 1). M1 markers are associated with decreased fibrotic cap thickness [21] and MMP12-producing plaque macrophages predict cardiovascular events and stroke incidence [22]. Moreover, although M2 plaque macrophages are not increased in plaques of acute myocardial infarction patients [23], M1 macrophages are more abundant in plaque material of infarction patients and of coronary artery disease patients [23,24,25*].

Much of the supportive data on plaque-specific macrophage polarization is based on in vitro experiments using single stimuli. However, the plaque harbors gradients of multiple stimuli, which, to complicate matters even more, depend on the plaque progression status [2**]. Therefore, it is difficult to define separate plaque macrophage subsets. Despite existing data on plaque macrophages and clinical outcome, a recent study failed to identify differences in M1 and M2 macrophages in early, late, unstable, or ruptured lesions, underlining that current classifications of plaque macrophages are too simplistic [26]. Rather than looking for polarized macrophages in the plaque, a more sensible approach may be to define the inflammatory phenotype of macrophages that are associated with a specific plaque region. For example, a recent study focused on macrophages found in calcified areas of the plaque and showed that they share many features with M2 macrophages [27].

Besides macrophages, also their precursor cells, monocytes, display heterogeneity. Human monocytes are subdivided based on their expression of CD14 and CD16. Classical monocytes express high levels of CD14 and no CD16 (CD14⁺ CD16⁻) and compromise the majority of total monocytes whereas nonclassical monocytes express CD16 and intermediate levels of CD14 (CD14⁺ CD16⁺). In addition, humans display also intermediate monocytes (CD14⁺CD16⁺) [28]. Experimental data from murine myocardial infarction models [29] suggest that M1 macrophages mainly originate from extravasated classical monocytes, whereas nonclassical monocytes share more features with M2 cells, albeit that conclusive evidence is currently lacking [28]. Moreover, the dynamics of postinfarct inflammation may not completely reflect the chronic low-grade inflammation that is typical of atherosclerosis, especially in humans. As can be appreciated from Table 2, most studies find positive relations between intermediate monocytes and cardiovascular outcome [30–41].

Based on the studies, summarized in Tables 1 and 2, both cardiovascular events and atherosclerotic plaque thinning tend to be associated with M1 polarized plaque macrophages and circulating intermediate CD14(+)+CD16(+) monocytes. This intermediate subset adhered much more avidly to endothelium than their classical and nonclassical antipodes, and this effect capacity augmented for monocytes from AMI patients, possibly owing to triglyceride induced CD11c integrin expression and clustering [36]. It is therefore tempting to speculate that, in addition to intraplaque cues, recruitment of intermediate monocytes contributes to a detrimental plaque macrophage signature, worsening clinical outcome. However, no mechanistic evidence is available to validate this hypothesis.

Table 2. Summary of studies linking circulating monocyte subsets with clinical outcome of cardiovascular diseases

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Subset</th>
<th>Outcome</th>
<th>n</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heine</td>
<td>2008</td>
<td>Intermediate monocytes</td>
<td>Predict CV events</td>
<td>94</td>
<td>[39]</td>
</tr>
<tr>
<td>Imanishi</td>
<td>2010</td>
<td>CD16+ monocytes⁺</td>
<td>Inverse association with fibrous cap thickness</td>
<td>40</td>
<td>[37]</td>
</tr>
<tr>
<td>Ikejima</td>
<td>2010</td>
<td>CD16⁻ monocytes⁻</td>
<td>Association with plaque ruptures</td>
<td>27 vs. 19</td>
<td>[38]</td>
</tr>
<tr>
<td>Rogacev et al.</td>
<td>2010</td>
<td>CD16⁻ monocytes⁻</td>
<td>† IMT</td>
<td>622</td>
<td>[33]</td>
</tr>
<tr>
<td>Poitou et al.</td>
<td>2011</td>
<td>Intermediate monocytes</td>
<td>Correlate with IMT changes during weight loss</td>
<td>36</td>
<td>[30]</td>
</tr>
<tr>
<td>Rogacev et al.</td>
<td>2011</td>
<td>Intermediate monocytes</td>
<td>Longitudinal Association with cardiovascular events</td>
<td>119</td>
<td>[31]</td>
</tr>
<tr>
<td>Rogacev et al.</td>
<td>2012</td>
<td>Intermediate monocytes</td>
<td>Cardiovascular Events prediction</td>
<td>951</td>
<td>[32]</td>
</tr>
<tr>
<td>Berg et al.</td>
<td>2012</td>
<td>Classical monocytes</td>
<td>Cardiovascular events prediction</td>
<td>659</td>
<td>[41]</td>
</tr>
<tr>
<td>Foster et al.</td>
<td>2013</td>
<td>Intermediate monocytes</td>
<td>† vcam-mediated adhesion</td>
<td>9 vs. 13</td>
<td>[36]</td>
</tr>
<tr>
<td>Zeng et al.</td>
<td>2014</td>
<td>Intermediate monocytes</td>
<td>Association with unstable angina</td>
<td>95 vs. 30</td>
<td>[33]</td>
</tr>
<tr>
<td>Winchester et al.</td>
<td>2016</td>
<td>Intermediate monocytes</td>
<td>Correlate with coronary artery calcification</td>
<td>72</td>
<td>[34]</td>
</tr>
<tr>
<td>Wildgruber et al.</td>
<td>2016</td>
<td>Intermediate monocytes</td>
<td>Restenosis prediction</td>
<td>67</td>
<td>[40]</td>
</tr>
</tbody>
</table>

*Intermediate and nonclassical.
Although human intermediate monocytes do not have a murine counterpart, they do share features with mouse classical monocytes, including high expression of CCR2, CCR5, and CX3CR1 [28,42]. Strong experimental evidence exists that Ly-6C<sup>hi</sup> classical murine monocytes preferentially accumulate in the vessel wall depending on CX3CR1, CCR2, and CCR5 [43,44], providing at least partial back up for this hypothesis. In line, senescent human intermediate monocytes increase their inflammatory phenotype and adhesive ability, possibly explaining the increased risk for cardiovascular diseases (CVD) with age [45].

**Impact of CVD risk factors and cognate drug interventions on plaque macrophage status**

Because of their high plastic capacity to adapt to the range of stimuli contained in the local microenvironment, plaque macrophages are likely responsive to metabolic risk factors and medication targeting these factors, with potential repercussions for disease progression. Over the past decade, this notion has been supported by several histopathological studies. Below we have outlined these phenotypic changes for the major risk factors and treatment thereof.

**Dyslipidemia**

This risk factor is a major modifier of monocyte and macrophage phenotype. A recent study by Stroes et al. [46] demonstrated lipid accumulation in circulating monocytes of familial hypercholesterolemia (FH) patients. This accumulation was accompanied by elevated CCR2 expression and ex-vivo chemotaxis in classical monocytes, suggesting augmented plaque invasion. These effects could be reversed by PCSK9 neutralizing therapy (alurcimab) to reduce plasma LDL levels. Although lipid accumulation by circulating monocytes was also observed in an FH mouse model (LDLR<sup>−/−</sup>), this was accompanied by defective migratory responses [47], without compromising endothelial adhesion and transmigration.

Lipid accumulation is also hallmarking the atherosclerotic macrophage. Sterols, fatty acids terpenes, and lysolipids can all interfere with macrophage functions by interacting with nuclear receptor family members, that are critical in macrophage homeostasis (e.g. FXR, LXR, ROR, N4Rs, and PPARs), as also outlined in numerous studies (reviewed in [48]). Apart from direct signaling, excessive cholesterol loading can induce endoplasmic reticulum stress and inflammasome activation, both acting proinflammatory. However, lipid laden foam cells were reported to have suppressed proinflammatory [49] or even profibrotic activity [50], both in vitro and in vivo, which was attributed to LXR activation by intracellular desmosterol.

Obviously, pharmacological correction of blood cholesterol levels, by statins, will have deep impact on plaque macrophages. Already in 2002, atorvastatin treatment was reported to change the inflammatory/thrombotic phenotype of carotid artery plaques [51] and these findings have been corroborated in several studies hereafter. As shown by Pastenkamp et al. [52], statin use is associated with smaller, more stable plaques (fewer macrophages, thrombi, calcification nodules). Even 3-month statin treatment of stroke patients dose-dependently could lower plaque macrophage content [53].

In keeping, the Fuster group reported sharply decreased atheroma formation, macrophage content, neoangiogenesis, and hemorrhage after statin treatment [54]. Carotid endarterectomy patients on atorvastatin therapy contained more CD68<sup>+</sup> macrophages, but paradoxically, this was associated with quenched rather than augmented intraplaque protease activity, Interleukin-6 expression, and enhanced fibrosis [55]. Whether statins effect these beneficial changes solely by their lipid lowering activity is unclear. Although statin effects have been reported to be LDL-C dependent [53], LDL independent modes have been proposed as well. Statins can target plaque inflammation and stabilize plaque, among others by inducing plaque galectin 3 expression [56], inhibiting the COX-2/mPGES axis [57] or by inducing PPAR<γ> [58], all known to drive macrophage polarization toward an anti-inflammatory phenotype. An in-depth study of lipid-dependent and lipid-independent mechanisms for statin effects on plaque macrophages are however still awaited.

**Hypertension**

A major risk factor for CVD, hypertension is routinely targeted in high-risk patients, by blocking angiotensin, adrenergic, or calcium channel signaling. Angiotensin-II signaling is reduced by angiotensin-I converting enzyme (ACE) or angiotensin II receptor 1A (AT1) receptor inhibition. Angiotensin therapy is expected to interfere with the activity of this subset for at least three reasons. First, carotid arteries contain detectable levels of ACE colocalizing with plaque inflammation [58]. Second, macrophages were seen to express key components of the angiotensin axis, including angiotensin II receptor type 1 (AT1) receptors. Finally, angiotensin II activation promotes lipid accumulation and migration, and shifts polarization towards the

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proinflammatory M1 phenotype [59]. Only a single study centered on the repercussions of angiotensin II-targeted therapy for human plaque macrophage status [60]: AT1 blockage (irbesartan) dampened COX-2/mPGES-1 dependent inflammation in plaque macrophages. Indeed, macrophage AT1 signaling induces cytokine and ROS production [60], and macrophage-specific AT1 deficiency increased phagocytic capacity and their resistance to apoptosis. Hence, AT1 blocking has an M2 polarizing effect, as was also observed in murine renal-injury induced atherosclerosis [59].

Signaling of macrophage adrenergic receptors, a second important target in antihypertensive therapy, also affects their inflammatory response. β-Adrenergic receptor activation favors M2 polarization, while suppressing M1 gene programs; conversely α-adrenergic signaling induces pro-inflammatory gene expression, an effect considered to be detrimental [61]. Although no human histology data are available to confirm this notion, this may plead in favor of the use of combined α/β instead of only β-selective adrenergic blockage. Regarding calcium channel blockers, a third major hypertension therapy target, data are inconsistent, although their use has been linked with increased carotid plaque progression in asymptomatic patients (n = 900 carotids) [62].

**Type 2 diabetes**

Although elevated glucose levels in patients with type 2 diabetes (T2D) may impact plaque macrophage function T2D status did not impact plaque macrophage content or lipid and SMC content in a medium-sized cohort [63]. Accordingly, despite a shift toward a more calcified plaque phenotype and higher a risk of future cardiovascular events in patients with T2D, Pasterkamp et al. [64] observed equivalent plaque macrophage content compared with plaques from patients without T2D. Plaque macrophages of patients with diabetes showed evidence of metabolic adaptations in glucose flux (as judged from the induced aldose reductase expression), which could potentially augment intracellular ROS and cytokine production [65*]. Moreover, hyperglycemia was shown to blunt M2 polarization, skewing macrophage phenotype toward a proinflammatory M1 phenotype in experimental atherosclerosis [66]. However, it is unclear whether, rather than total macrophage content, macrophage polarization status is related to T2D.

Conversely, numerous studies documented that lowering glucose levels with metformin has significant antiinflammatory activity. Metformin reduced maximal, not mean intimal stenosis (cIMT) in (type 1) diabetics [67**], whereas in patients without diabetes it failed to reduce mean cIMT, despite lowering HBA1c and glucose levels [67**]. DPP-4, another preferred target in diabetic therapy, is downregulated during monocyte–macrophage differentiation and only scarcely expressed in plaques, by microvascular endothelium [67**]. Its inhibition was reported to act immune-suppressive, potentially by dampening NF-κB and AP-1 transcriptional activity [68*]. Based on these data and its atheroprotective activity in a diabetic mouse model of atherosclerosis, favorable effects of DPP4 inhibition on plaque macrophages are to be expected. However, histological proof is awaited.

**Outstanding questions**

From the above overview one may conclude that our understanding of human macrophages and their precursors in atherosclerosis-related IHD is limited, and most studies are of descriptive nature. A first open question involves the plaque macrophage origin; whether macrophages are derived from invading monocytes [2**] or from expanding resident macrophages (as proposed in recent experimental studies [69**]). Plaque macrophage origin will have major implications for the effectiveness of chemotaxis-targeting therapies. Currently, little is known about the quantitative role of proliferating resident macrophage on plaque progression compared to recruitment of circulating monocytes, and in particular of intermediate monocytes. In addition, vascular smooth muscle cells also have been described to transdifferentiate into macrophages, contributing to plaque macrophage burden [70].

The current literature (Tables 1 and 2) suggests that circulating intermediate monocytes are linked to proatherogenic macrophage subsets in human plaque. To delineate such a relationship, there is a need for studies that simultaneously assess plaque macrophage phenotype and circulating monocyte subsets in an individual patient (as we recently showed for adipose tissue macrophages [71*]). To unravel the developmental origin of plaque macrophages and their contribution to plaque growth and phenotype, we are most likely confined to murine models.

A second challenge concerns macrophage heterogeneity. Although this has been well established for many tissues in healthy and diseased situations, hardly any quantitative data on spatiotemporal dynamics and impact of environmental factors (such as diet/medication) on macrophage subset profiles are available for human atherosclerosis [26*]. Given the high functional diversity of macrophage subsets, a better definition of macrophages species most correlated with an adverse disease progression will
be indispensable for tailored intervention or imaging measures. At present, the conventional cell separation techniques, such as fluorescence-activated cell sorting, fall short to discriminate macrophage subsets in human plaque. This is, among others, due to the intrinsically high autofluorescence, the large bandwidth in size and density of plaque macrophages, to the high plaque content of cell debris, to selection bias of current markers, and to the need of aggressive tissue dissolution strategies. The use of mass cytometry or single cell sequencing techniques could at least partly circumvent this setback.

A third challenge relates to the macrophage microenvironment. As described above, macrophages adapt to their local (and indirectly to the global) context. Identification of the culprit components in the plaque microenvironment, which drive adverse macrophage functions in disease progression, will obviously provide unprecedented opportunities to steer or reconstruct detrimental macrophage populations in plaque by drug or dietary intervention. MRI and ex-vivo studies on tissue biopsies, could pave the way to such identification.

CONCLUSION

As outlined in this review, numerous studies have highlighted the importance of macrophages and their precursor monocytes in atherosclerosis related IHD. Monocytes and in particular intermediate monocytes were correlated with disease progression and incidence of clinical events. For macrophages, data are rather inconsistent, implying that macrophage location seems more relevant than mere content. Interestingly, the more widespread use of stringent medication, such as statins, antihypertensives, and antiangiobiotics, has impacted macrophage status and numbers in plaques, and this might have been instrumental in the gradual shift from rupture prone plaque phenotype toward more fibrotic and calcified, but also erosion-prone plaques as Pasterkamp et al. [46] have shown.

The present review also underpins the relevance of a better definition of the direct microenvironment and phenotype of macrophages, as such information will be pivotal in developing a macrophage-targeted intervention strategies that are effective at all stages of disease, and do not compromise beneficial macrophage functions in injury repair or host defense.

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KW: Netherlands Heart Foundation (2013T143)

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

■ of outstanding interest


This review provides good insight in the different stimuli that are present in the atherosclerotic plaque and can influence resident macrophages.


Diabetes adversely affects macrophage polarization in human atherosclerosis

Macrophage complexity in human atherosclerosis

Bissoon and Wouters
This paper describes direct anti-inflammatory effects of DPP-IV inhibitors via NF-kB.
Important review on the recent discoveries on murine tissue macrophage origin and ontogeny.

This paper was the first to measure different immune cell populations in blood and both visceral and subcutaneous adipose tissue of lean and obese individuals, showing that M1 macrophages in visceral adipose tissue are associated with circulating classical monocytes.