**EDITORIAL COMMENT**

**Monocyte Diversity in Myocardial Infarction**

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A key role for monocyte-derived macrophages for the development, progression, and destabilization of atherosclerotic plaques has long been recognized. However, the scale of relatively focal macrophage activity in the plaque changes dramatically after atherothrombotic complications. While local proliferation ensures renewal and maintenance of many macrophage cardiac pools under steady-state conditions, prolonged acute ischemia and tissue injury in myocardial infarction (MI) attracts massive amounts of monocytes from circulation. The biological aim of this response is to promote healing of the damaged myocardial tissue by the removal of dead cells, replacement of necrotic areas by connective tissue, remodeling of myocardial structure and geometry to compensate cardiomyocyte loss, and ultimately, to restore cardiac vascularization, at least at a microvascular level. Indeed, circulating monocytes and their tissue descendants, the macrophages, produce myriad cytokines orchestrating various processes of myocardial repair (1,2). However, an imbalance in this process may result in unfavorable remodeling with the development of cardiac impairment, eventually leading to heart failure in some patients despite a successful and prompt restoration of blood flow by coronary intervention (3).

**Monocyte populations.** Circulating monocytes are not uniform and include subsets with profoundly different characteristics. At present, monocyte populations are commonly described on the basis of the expression of the lipopolysaccharide receptor CD14 and Fc receptor γIII (CD16). Although the differential monocyte populations may have implications for the pathogenesis of atherosclerosis, it is not yet clear how they may do so, for example, by different expression of lipoprotein scavenger receptors and/or inflammatory characteristics.

A major subset (~85%) of large, high-density CD14+/CD16– monocytes co-expressing CD64 represent potent phagocytes, and produce large amounts of proinflammatory cytokines (for example, interleukin-1, interleukin-6), reactive oxygen species, and prostaglandin E2 (4). In addition, CD14–/CD16– monocytes are active producers of plasminogen activator (5).

In contrast, a smaller (<15%) subset of smaller, less dense CD16+ (usually CD14low) monocytes produces more interferon-α and exhibits potent antigen-presenting capacity. Despite lower expression of CD14, the expression of toll-like receptor-4 (an essential coreceptor for CD14) is 2.5-fold higher on CD14low/CD16– monocytes, which are highly active in the production of tumor necrosis factor α and interleukin-12 (6).

In addition to the CD14+CD16– and CD14low/CD16+ monocyte populations described in the preceding text, there is a monocyte population (~5% of all monocytes) that is both CD14+CD16+. These CD14+CD16+ monocytes can be mobilized in a catecholamine-dependent manner, with a 4-fold increase in quantity after intensive physical exercise (7). However, physically active subjects have a lower percentage of CD14+CD16+ monocytes, which is associated with levels of tumor necrosis factor α (8). The CD14+CD16+ monocyte counts positively correlate with levels of atherogenic lipids and negatively correlate with high-density lipoprotein cholesterol levels (9). Patients with coronary artery disease have higher numbers of CD14+CD16+ monocytes than do healthy subjects (10). Of note, the patients with the highest proportion (namely, upper quartile) of CD14+CD16+ monocytes have an odds ratio of 4.9 (95% confidence interval: 2.5 to 19.1) for coronary artery disease, even after adjusting for other confounding factors such as diabetes mellitus, hypertension, and lipid profile (10).

**Monocyte populations in myocardial infarction.** As highlighted in this issue of the Journal, Tsujioka et al. (11) demonstrated specific dynamics of monocyte subsets after presentation with an acute myocardial infarction (AMI). They found that the magnitude of CD14+CD16– monocyte mobilization was associated with a marker of cardiac recovery (myocardial salvage), but CD14+CD16+ counts had no impact on cardiac recovery, and the biological role of the observed dynamics of their number remains unclear. Further insight into the role of monocyte subsets in MI may be possible by putting the observations of Tsujioka et al. (11) in the context of previous experimental findings.

In an experimental study, Nahrendorf et al. (12) revealed that circulating levels of Ly-6C+ cells (a mouse analogue of CD14+CD16– monocytes) closely corresponded to their myocardial levels, which constituted 78% of myocardial monocytes and macrophages early after MI onset. This monocyte subset was shown to exhibit phagocytic, proteolytic, and inflammatory properties, as well as being able to digest necrotic myocardium (12). Similarly, Tsujioka et al.
(11) demonstrated high and exclusive expression of the monocyte chemoattractant protein (MCP)-1 receptor CCR2 by the CD14⁺CD16⁻ monocytes. Importantly, plasma MCP-1 levels are known to increase as early as 3 h after the onset of chest pain, and reach their maximum at 24 h, with further gradual decline (13). Putting together the clinical data on such early secretion of MCP-1 and the prompt up-regulation of CCR-2 expressing CD14⁺CD16⁻ monocytes—as demonstrated by Tsujioka et al. (11)—with other experimental evidence that cardiac mobilization of these cells closely depends on cardiac MCP-1 synthesis and secretion, we can perhaps improve our understanding of the pathophysiological role of MCP-1 in regulation and monocytosis during the early phase of MI.

However, does this monocyte population have any significance beyond phagocytosis of damaged myocardium? Interestingly, MCP-1 contributes to the development of coronary collaterals during the early phase of AMI and experimental MCP-1–stimulated neovascularization, independently from bone marrow endothelial progenitor cell involvement. Such interactions may indicate a possible link between MCP-1–dependent CD14⁺CD16⁻ monocyte mobilization and myocardial angiogenesis (14,15). Indeed, human monocytes include a population of cells able to obtain an endothelial cell phenotype in culture, and these probably constitute a major population of circulating endothelial progenitors and cells expressing vascular endothelial growth factor receptors (VEGFR2) (16–18). Additionally, monocyte-derived progenitors are able to successfully restore left ventricular function after experimental MI, and the number of circulating CD14⁺/VEGFR2⁺ cells is significantly increased in AMI (19,20). We have also observed that one-third of CD14⁺CD16⁻ monocyte express receptors to VEGF (VEGFR1), compared to only ≈8% of CD14⁻CD16⁻ monocytes and in contrast to the extremely high expression (up to 90%) of VEGFRI by a subset of CD14⁺CD16⁻ monocytes (Fig. 1).

Nonetheless, MCP-1 levels determined during admission of 2,270 patients with acute coronary syndrome who were enrolled in the OPUS–TIMI 16 (Orbofiban in Patients With Unstable Coronary Syndromes–Thrombolysis In Myocardial Infarction 16) trial (21) were independently associated with an increased risk of death or MI during 10 months of follow-up, perhaps indicating that an unbalanced MCP-1 overexpression may have a negative impact on the recruitment of proinflammatory CD14⁺CD16⁻ monocytes, thus resulting in impaired myocardial recovery—which has essentially been confirmed by Tsujioka et al. (11).
In contrast to CD14+CD16− monocytes, Tsujioka et al. (11) found that the increase in the number of CD14+CD16+ cells was delayed and was not associated with any marker of cardiac outcome. Of note, given the initial decrease in the number of circulating CD16+ cells (as compared with stable coronary artery disease), it appears that the consequent increase in their levels might simply reflect a return to the initial count. Similarly, in an experimental model of MI, no significant changes in the circulating levels of Ly-6CΔ (mouse analogues CD14+CD16+ monocytes) were observed. Despite this, the number of CD14+CD16+ monocytes in the myocardium increases dramatically in the second phase of MI, and these cells are recruited de novo from the circulation, constituting ≈80% of myocardial monocytes and macrophages (12). Furthermore, Nahrendorf et al. (12) have shown that although circulating levels were not affected, their capacity to migrate into myocardium increased 4.8-fold. These data, therefore, indicate that a simple count of CD14+CD16+ monocytes in the circulation may not accurately reflect their cardiac activity, and additional changes in functional characteristics (e.g., receptor expression) and/or high levels of certain cytokines/chemoattractants may be responsible for their selective mobilizations.

Interestingly, CD14+CD16+ monocytes fail to migrate in response to CCL2 in vitro, consistent with the absence of MCP-1 receptors on these cells (22), as demonstrated by Tsujioka et al. (11). However, CD14+CD16+ monocytes exclusively express fractalkine receptor CX3CR1, and fractalkine levels reportedly decrease only in the early phase of MI and are restored by the time of active CD14+CD16+ monocyte recruitment (12,23). Although CX3CR1 was essential for CD16+ monocyte homing, this receptor alone cannot explain the enhanced selective migration of CD16+ monocytes, as it is equally expressed (strongly) on cells both in the stable situation (namely, in healthy controls) and in disease (MI), thus indicating that other receptors should simultaneously be involved in this process. Indeed, CD14+CD16+ monocytes show enhanced expression of CCR5 and stromal cell derived factor (SDF-1) receptors CXCR4, as well as a high migratory activity in response to SDF-1 and macrophage inflammatory protein-1α (RANTES) (22,24).

Although the role of CD14+CD16+ monocytes in MI remains obscure, mouse analogues of these cells have proangiogenic properties and selectively express higher levels of VEGF, a well-recognized potent regulator of angiogenesis (12). Expression of receptors for proangiogenic SDF-1 may also be of similar importance (25,26). In a mouse experimental model, macrophage colony-stimulating factor reduces the infarct area and improves left ventricular remodeling after MI, through the recruitment of CXCR4+ cells into the infarcted myocardium (26).

These important findings may serve as a basis to provide some explanation for one of the existing monocyte-related controversies, that is, monocytes are required for successful myocardial recovery—but monocyte infiltration and high levels of MCP-1 may be associated with negative outcomes. This controversy may stem from the excessive (or prolonged) secretion of monocyte chemoattractants and abnormal monocyte recruitment into myocardium, thus causing an imbalance in the reparative and negative monocyte properties. Clearly, further studies are warranted to better understand the monocyte role in post-MI myocardial recovery.

**REFERENCES**


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