The role of monocyte phenotype switching in peri-procedural myocardial injury and its involvement in statin therapy

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Peri-procedural myocardial injury, which is associated with worse long-term clinical outcome, is a common complication related to inflammatory pathogenetic mechanisms. Monocytes and macrophages play key roles in the initiation and progression of atherosclerosis. Recent studies have demonstrated that monocytes in human peripheral blood are heterogeneous, including CD14⁺CD16⁻ monocytes and CD14⁺CD16⁺ monocytes. Several lines of evidence suggested that CD14⁺CD16⁺ monocytes might contribute to the accelerated atherosclerosis. In view of the heightened appreciation of the heterogeneity of circulating monocytes, we hypothesized that an up-shifting subset of CD14⁺CD16⁺ monocytes might be induced by percutaneous coronary intervention (PCI), which subsequently leads to peri-procedural myocardial injury. Moreover, statins loading before PCI could exert anti-inflammatory effects partly by modulating monocyte phenotype and thus prevent peri-procedural myocardial injury.

Key words: monocyte subsets • inflammation • peri-procedural myocardial injury • statin

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**Background**

Percutaneous coronary intervention (PCI) is commonly used in patients with coronary heart disease (CHD) for revascularizing culprit vessels and for restoring myocardial blood supply. However, myocardial infarction (MI) during coronary intervention occurs in 10–40% of cases and is often associated with even worse outcome observed in long-term follow-up. PMI still negatively affects a considerable proportion of patients [1], although standard pre-procedure administration of statins and antiplatelet agents, along with interventional strategies of thrombus aspiration, filter devices, and improved procedural techniques, have drastically reduced the incidence of peri-procedural myocardial injury (PMI). The causes and pathogenesis of this complication are multifactorial, and the exact mechanism is not clearly understood.

It is believed that PMI is related to inflammatory pathogenetic mechanisms. The process of stent implantation triggers a cascade of events within the vessel wall and myocardium, as well as systemically, that leads to a direct deleterious effect on cardiac myocytes extending myocardial necrosis. Micro-infarctions inherently instigate an inflammatory process characterized by leukocyte (monocyte and macrophage) infiltration [2]. This in turn amplifies a series of local inflammatory events. Monocytes and macrophages play key roles in the initiation and progression of atherosclerosis. Evidence from animal models has confirmed that reduction in circulating monocytes can effectively suppress plaque development [3]. Clinical data has also shown that monocytosis is associated with cardiovascular disease and atherosclerotic plaque burden [4,5]. Importantly, Fukuda et al. demonstrated that circulating monocyte level increased after coronary stent implantation [6]. Meisel et al. further showed that peak monocyte count had a significantly positive correlation with peak CK level [7]. These findings indicate that circulating monocyte level likely influences the incidence and magnitude of PMI.

Recent studies have demonstrated that monocytes in human peripheral blood are heterogeneous [8]. Basically, the expression of CD14 and CD16 mainly distinguishes 2 monocyte subsets: CD14+CD16- monocytes and CD14+CD16+ monocytes. Cumulative evidence has suggested that CD14+CD16- monocytes rather than CD14+CD16+ monocytes are involved in the pathogenesis of atherosclerosis in humans [9–12]. However, there is no report investigating the relationship between circulating monocyte subsets and PMI in patients with elective PCI.

In developing this study, we considered the following facts: (1) inflammation plays a pivotal role in the development of PMI; (2) implantation of a stent induces an elevation in monocyte level; (3) elevated monocyte level is associated with the extent of PMI; and (4) CD14+CD16- monocytes, also termed pro-inflammatory monocytes, contribute to accelerated atherosclerosis. Thus, we propose that PCI might give rise to a phenotypic transition of circulating monocytes toward CD14+CD16- monocytes, which might further lead to PMI. It is reasonable to deduce that treatment with statins prior to PCI is clinically beneficial due to its monocyte phenotype modulation function.

**Monocyte Heterogeneity**

Monocyte heterogeneity is conserved in mice and humans [8]. In mice, monocytes are divided into 2 subsets, mainly according to Ly6C antigen expression: Ly6C^high CX3CR1^low CCR2^high monocytes and Ly6C^low CX3CR1^high CCR2^low/mid^monocytes [8]. Ly6C^high monocytes are termed “inflammatory” in deteriorating disease and inflammatory progress. Conversely, Ly6C^low monocytes are referred to as “resident” due to their capacity to accumulate regardless of inflammation. They patrol the vasculature, initiate rapid immune response following injury or infection, and support tissue repair [13,14]. Likewise in humans, originally, the differential expression of CD14 and CD16 on monocytes could define 2 subsets of monocytes: CD14+CD16- monocytes and CD14+CD16+ monocytes [8]. These cells also display distinct profiles of chemokine-receptor expression, potentially reflecting different recruitment properties. For example, CD14+CD16- monocytes express a high level of CCR2, whereas CD14+CD16+ monocytes possess high levels of CX3CR1 and CCR5 receptors. CD14+CD16- monocytes are traditionally described as “pro-inflammatory” monocytes, which account for only 5% to 15% of the monocyte pool in the steady state. They are characterized by higher major histocompatibility complex (MHC) class II and proinflammatory cytokines expression (e.g., TNF-α) in comparison to CD14+CD16+ monocytes [15]. In addition, they have been observed to increase in various stress or disease conditions [16]. More recently, a CD14^hi^monocyte subset (lacking CD14, but expressing CD16) was identified as the human patrolling monocyte with distinct function properties compared to CD14+CD16- monocyte [17]. They exhibit patrolling behavior similar to that of murine Ly6C^hi^monocytes. Additionally, they do not respond to LPS, but respond to viruses and endogenous nucleic acids via TLR7 and TLR8, and thus may be important in anti-viral immunity. This finding provides evidence that human monocytes correspond to their mouse counterparts, making it possible to better interpret results from murine models that closely mimic human diseases [18]. Collectively, monocyte subsets may have specific roles in the onset and development of inflammatory diseases, including atherosclerosis.

**The Role of Monocyte Subsets in Atherosclerosis**

Atherosclerosis is a chronic inflammatory disease characterized by the accumulation of lipids and leukocytes in the arterial vessel wall [19]. Monocytes are the first and major participant in...
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Atherosclerosis [20]. They play critical roles in the initiation and progression of atherosclerosis [21]. Recently, monocytes have been observed to be heterogeneous. In humans, the disturbed balance of monocyte subsets has been linked to various diseases [16], indicative of the importance of the sophisticated monocyte subset ratio. Similarly, the role of each monocyte subset in atherosclerosis has also been investigated in animal experiments and human trials.

A series of experiments have shown that Ly6C<sup>high</sup> monocytes progressively increase in circulation and subsequently preferentially adhere to activated endothelium, infiltrate lesions, and give rise to atherosclerotic macrophages. Swirski et al. first reported that hypercholesterolemia induced a drastic expansion of blood Ly6C<sup>high</sup> monocytes, but not Ly6C<sup>low</sup> cells in ApoE-deficient mice fed a high-fat diet [22]. They also established a direct link between circulating Ly6C<sup>high</sup> monocytes and lesional macrophages. These findings suggest that a cholesterol-rich diet may promote murine atherogenesis partly due to the increase of Ly6C<sup>high</sup> monocytes. Hyperhomocysteinemia (HHcy), another potent risk factor for CVD [23], has also been shown to modulate monocyte heterogeneity and thus lead to atherosclerosis. By using murine models of severe HHcy and hypercholesterolemia, Zhang et al. reported that HHcy could promote inflammatory monocyte subset differentiation and their accumulation in atherosclerotic lesions via NAD(P)H oxidase-mediated oxidant stress, which was independent of hyperlipidemia [24]. The result indicated that HHcy-induced inflammatory monocyte subset differentiation might be responsible for the increased risk of CVD in HHcy. Accordingly, specific targeting of inflammatory monocyte has also been associated with attenuated atherosclerosis. Inflammatory monocytes (Ly6C<sup>high</sup> monocytes), but not the non-inflammatory subset (Ly6C<sup>low</sup> monocytes), depend on the chemokine receptor CCR2 to accumulate in injured tissue. More recently, Leuschner et al. first demonstrated that monocyte-targeting siRNA nano-materials could silence CCR2 mRNA in the Ly6C<sup>high</sup> monocyte subset and thus reduce regional recruitment of these cells in atherosclerotic plaques, which consequently reduced the infarct size after coronary artery occlusion [25]. In addition, it has recently been shown that the splenic monocyte population may represent a potential therapeutic target for any anti-inflammatory strategy focusing on inflammatory monocytes. The spleen, recognized as a reservoir of undifferentiated monocytes, may contribute to the development of atherosclerosis via induction of Ly6C<sup>high</sup> monocytes [26]. Robbins et al. recently demonstrated that the spleen plays a role in supplying Ly6C<sup>high</sup> monocytes to growing atheroma in response to hypercholesterolemia [27]. They also proved that by eliminating this splenic source, lesions became less cellular.

Conversely, there remains some controversy as to what extent circulating Ly6C<sup>high</sup> monocytes could increase in atherosclerosis. Some studies reported that the numbers of this subset remained relatively unchanged [22,28], whereas others observed an increase of Ly6C<sup>low</sup> monocyte level [29]. Also, little is known about their exact functions in disease progression. Based on previous studies on the anti-inflammatory role of Ly6C<sup>low</sup> monocyte, it is proposed that this subset may promote a more ‘stable’ lesion, if not necessarily a smaller one [30]. However, decisive experimental evidence in support of this is currently lacking. More research is required to address how these subsets are controlled and how they participate in the development of atherosclerosis.

Whereas some of the studies mentioned above have investigated monocyte subsets in experimental murine models, the role of monocyte subset in humans is unclear. Knowledge of human monocyte subsets is relatively limited to observational studies. A study of the respective blood monocytes revealed that CD14<sup>+</sup>CD16<sup>+</sup> monocytes correlated negatively with the concentration of HDL, but positively with levels of atherogenic lipids in patients with hypercholesterolemia [9]. Schlitt et al. showed an elevated level of CD14<sup>+</sup>CD16<sup>+</sup> monocytes in patients with coronary artery disease (CAD) in comparison with a health cohort [10]. They also found that the increase of CD14<sup>+</sup>CD16<sup>+</sup> monocytes is an independent risk factor for CAD, indicating that these cells might participate in disease progression. In line with this, this subset has been related to higher cardiovascular risk in both low- and high-risk subjects [31–33]. Furthermore, Imanishi et al. first showed that there is a correlation between an increased relative proportion of CD14<sup>+</sup>CD16<sup>+</sup> monocytes and the presence of vulnerable plaques in patients with stable angina pectoris, as well as unstable angina pectoris(UAP) [11,12]. These results suggest that the shift in monocyte subsets may be relevant to the development of atherosclerosis, especially coronary plaque vulnerability. However, the mechanisms controlling monocyte polarization in atherosclerosis remain unclear.

**Monocyte Phenotype may be Related to Macrophage Phenotype**

There is a growing body of evidence that changes in monocyte subpopulations may be involved in the development of atherosclerosis and its complications in humans. Diverse macrophage phenotypes derived from these monocyte subsets in response to different stimulus have also been identified in atherosclerotic lesions [34,35]. ‘M1’ cells (or “classically activated proinflammatory” macrophages), which derive from monocytes in *in vitro* culture with inflammatory stimuli such as interferon-γ and LPS, are associated with proinflammatory cytokine production and cellular immunity. ‘M2’ cells (or “alternatively activated reparative” macrophages), raised by stimulating their progenitors with cytokines typically involved in the resolution of inflammatory responses (e.g., IL-4 and IL-13), are associated with the chemokine receptor CCR2 to accumulate in injured tissue.
with tissue repair and humoral immunity [8]. In vivo, these cells may be distinguished by the unique makers they express.

Khallou-Laschet et al. showed that lesion progression is associated with the predominance of the M1 over the M2 phenotype in ApoE-deficient mice [36]. M1- and M2-like macrophages also coexist in human atheromas [37]. Waldo et al. demonstrated that human monocytes could differentiate into macrophage subpopulations with different gene expression patterns and thus different potentials for promoting atherosclerosis [35]. The GM-Mac phenotype that predominates in normal intima expresses genes involved in reverse cholesterol transport and macrophage emigration from the vessel walls. Conversely, the M-Mac phenotype that predominates in diseased intima expresses many pro-inflammatory genes. These findings indicate that macrophage subpopulation skewing may affect atheroma evolution and outcome. Interestingly, a variety of macrophage phenotypes may derive from different monocyte subsets [15]. In concordance with this hypothesis, previous studies have demonstrated Ly6C<sup>hi</sup> monocytes that dominated during phase I following MI exhibited inflammatory activity and promoted digestion of infarcted tissue, whereas Ly6C<sup>lo</sup> monocytes that accumulated later displayed a more regulatory function and propagated myocardial healing in a murine model of coronary ligation [14]. This finding was also duplicated in studies of patients with acute MI, which showed a similar biphasic monocyte response [38]. However, direct evidence is still lacking to establish that Ly6C<sup>hi</sup> monocytes selectively give rise to M1 macrophages, whereas Ly6C<sup>lo</sup> monocytes give rise to M2 macrophages. Cell tracking studies are needed to investigate the link between monocyte subsets and macrophage phenotypes in more detail. Overall, it is currently believed that the heterogeneity in macrophages within atherosclerotic plaque is derived both from the heterogeneity of the originating monocytes and the inflammatory and lipidic stimuli available in the plaque.

## Monocyte Subset and Peri-procedural Myocardial Injury

PMI is common after PCI. It can result from procedural complications of PCI such as occlusions of side branches, dissection, distal embolization, and no-reflow phenomenon [39]. Of note, PMI can also occur silently after uneventful PCI procedures, which is generally the case in the vast majority of patients with elevated biomarker levels after PCI [40].

Inflammation may play a significant role in the development of PMI. Implantation of a stent inherently causes mechanical disruption of the vessel wall and incites an inflammatory process within the atherosclerotic blood vessel [41]. In addition, PCI provokes plaque fissure and then leads to distal embo- lization of plaque micro-debris. This phenomenon produces micro-infarctions that instigate an inflammatory process characterized by leukocyte (monocyte and macrophage) infiltration [2]. Besides the local action in the vessel wall and damaged myocardial region, there is also a systemic inflammatory response characterized by elevated CRP and interleukin-6 levels post-PCI in clinical studies [42,43]. Patients with significant troponin release after percutaneous transluminal coronary angioplasty (PTCA) had higher inflammatory markers in circulation than those without troponin release after the procedure [44]. Therefore, the process of stent implantation may trigger exaggerated inflammatory responses, including activation and recruitment of leukocytes and platelets to the site of lesion and thus result in a direct deleterious effect on myonecrosis, suggesting that inflammation is one of the mechanisms of PMI.

Notably, circulating monocytes and lesional macrophages actively participate in the post-PCI inflammatory process [45]. Fukuda et al. reported that circulating monocyte level increased after coronary stent implantation [6]. Meisel et al. [7] showed that peak monocyte count shared the same tendency with peak CK level, indicating circulating monocyte level was likely related to the extent of PMI.

As described above, in view of the heterogeneity of monocytes, a growing body of literature points to a subset-specific contribution of monocytes to atherogenesis. Importantly, accumulating evidence suggests that monocytes may exert distinct functions in the setting of MI by virtue of subset heterogeneity.

Nahrendorf et al. identified a sequential mobilization of different monocyte subsets in mouse MI, due to orchestrated release of subset-specific chemokines [14]. They suggested that distinct monocyte subsets may contribute in specific ways to myocardial ischemic injury in mice, underscoring the need for a balanced and coordinated monocyte response. Likewise, in humans, Tapp et al. observed the differential dynamics of human monocyte subsets following ST-elevation myocardial infarction (STEMI) [46]. The count of CD14<sup>-</sup>CD16<sup>+</sup> monocytes increases dramatically in the acute phase after MI, and correlates with peak troponin level and left ventricular ejection fraction (LVEF) at 6 weeks. Notably, CD16 expression by CD14<sup>-</sup>CD16<sup>+</sup> monocytes could uniquely and independently predict 6-week LVEF. Thus, these findings demonstrate a close relationship between CD14<sup>-</sup>CD16<sup>+</sup> monocytes and the degree of myocardial damage and recovery after STEMI. Interestingly, they also identified a long-term increase in monocyte platelet aggregates (MPAs) count following STEMI, which was associated with myocardial injury suggesting that activated platelets might be involved in the modulation of monocyte phenotype and function, and providing a link between the inflammatory status of monocytes and the extent of microvascular obstruction.

Several studies suggested that monocyte-platelet interaction could induce a pro-inflammatory phenotype in circulating...
monocytes. Passacquale et al. first identified that circulating CD14+CD16+ monocyte was regulated by platelet activation and consequent formation of MPA [47]. Healthy subjects receiving influenza immunization displayed an expansion of circulating MPA and a shift in circulating monocytes towards CD16+. In vitro studies showed that monocyte-platelet interaction led to a phenotypic change of CD14+CD16+ monocytes towards CD14+CD16+. Thus, the findings indicate that acute inflammation might induce an increase in inflammatory monocytes via platelet activation and subsequent MPA. Notably, in the setting of PCI, mechanical injury could cause inflammation, but also promote activation of platelets due to endothelial denudation, medial dissection, and exposure of sub-endothelial matrix proteins to inflammatory mediators [48,49]. Gasperetti et al. showed an increase of platelet aggregation during PTCA in coronary sinus blood during angioplasty [50]. In addition, Serrano et al. confirmed an increase in monocyte activation and formation of platelet-leukocyte aggregates in the setting of PTCA procedures [51]. Based on these observations, we speculate that PCI might induce a pro-inflammatory phenotype in circulating monocytes via inflammatory stimulus, especially platelet activation, contributing to microvascular and myocardial injury in the setting of PCI.

Effect of Statin on Monocyte Phenotype Switching Might Contribute to its Protective Role in Peri-procedural Myocardial Injury

Because PMI is related to inflammatory pathogenetic mechanisms, therapies directed to atherosclerotic and inflammatory processes may help. Recently, several randomized clinical trials have shown that acute loading of statins prior to PCI could mitigate PMI [52–54]. The mechanism of improved clinical outcomes with statins has been associated with ‘pleiotropic’ effects beyond LDL lowering, which might counteract the inflammatory and prothrombotic milieu caused by PCI [55].

The potential beneficial effect of statin on cardiovascular-related diseases has been investigated in several clinical and animal studies [56,57]. Although the specific mechanisms by which statin treatment elicits this effect have yet to be elucidated, some studies have suggested that statin might exert an uncharacterized immunomodulatory effect on modification of the phenotype of peripheral blood monocytes. The initial observation reported a statin-induced shift in CD14+CD16+ monocytes frequencies in hypercholesterolemic patients with fluvastatin treatment [58]. However, several subsequent studies have reached the opposite conclusion and suggest that statin might suppress the development of inflammatory monocytes.

Swirski et al. first demonstrated that statin administration partially reversed Ly6C<sup>hi</sup> monocytosis during experimental atherosclerosis in vivo [22]. Several clinical studies also support a negative influence of statins on inflammatory monocyte frequencies. Imanishi et al. reported that an increase in CD14+CD16+ monocyte was observed in a control group of patients with UAP, but it remained stable in patients with statin treatment [11]. They suggested that statin might have the potential to reduce CD14+CD16+ monocytes, thus increasing the tension of the fibrous cap in vulnerable plaques. This is consistent with a recent findings that statin administration was associated with low numbers of CD14+CD16+ monocytes in patients following heart transplantation [59]. In addition, rosuvastatin therapy combined with exercise training significantly inhibited CD14+CD16+ monocyte percentages [60].

Based on these observations, we suggest that the anti-inflammatory effect of statins might also participate in the suppression of inflammatory monocyte levels. As noted above, inflammatory monocytes are associated with myocardial injury and microvascular obstruction, which are potential contributors to PCI-related or peri-procedural myocardial infarction. Without direct evidence demonstrating the impact of statin on monocyte phenotype during PCI, we speculate that it might influence inflammatory monocyte frequencies and lead to a reduction of peri-procedural cardiac marker release during PCI.

Future Directions

This hypothesis provides a new insight into monocyte subset and PMI, and suggests phenotypic transition of monocytes as a novel therapeutic strategy against PMI. To test the hypothesis, we designed a prospective comparative study, using a high loading dose atorvastatin before PCI, to assess the relationship between monocyte subsets and PMI or PMI-related outcomes, and to observe the effect of loading dose atorvastatin on monocyte phenotype in patients undergoing elective PCI. Our preliminary results demonstrated a moderate association between increased inflammatory monocytes and myocardial injury induced by PCI (data not shown). There was also a tendency to higher post-PCI frequencies of CD14+CD16+ monocytes in the control group than in the loading dose group. However, further studies, especially large-scale clinical trials, are needed to confirm our hypothesis.

Conclusions

We propose that phenotypic switching of monocytes might be induced by PCI and this might contribute to the pathophysiology of PMI. Loading of statins prior to PCI might exert anti-inflammatory effects partly by modulating monocyte phenotype, which limits PMI. Although this hypothesis requires preliminary experiments before proceeding to large-scale trial, phenotypic transition of monocytes could be a promising treatment strategy that could shed light on the protection from PMI.
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