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Monocytes in Myocardial Infarction

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Abstract

Myocardial infarction (MI) is the leading cause of death in developed countries. Though timely revascularization of the ischemic myocardium and current standard therapy reduce acute mortality after MI, long-term morbidity and mortality remain high. During the first 1 to 2 weeks after MI, tissues in the infarcted myocardium undergo rapid turnover, including digestion of extracellular matrix and fibrosis. Post-MI repair is crucial to survival. Monocytes recruited to the infarcted myocardium remove debris and facilitate the repair process. However, exaggerated inflammation may also impede healing, as demonstrated by the association between elevated white blood cell count and in-hospital mortality after MI. Monocytes produced in the bone marrow and spleen enter the blood after MI and are recruited to the injured myocardium in 2 phases. The first phase is dominated by Ly-6c^{high} monocytes and the second phase by Ly-6c^{low} monocytes. Yet the number of Ly6C^{low} monocytes recruited to the infarct is much lower, and Ly6C^{high} monocytes can differentiate to Ly6C^{low} macrophages in later healing stages. Understanding the signals regulating monocytosis after MI will help design new therapies to facilitate cardiac healing and limit heart failure.

Keywords

monocytes; macrophages; hematopoiesis; myocardial infarction

Monocytes

The innate immune system initiates defense against microorganisms quickly and efficiently, and monocytes are innate immunity's major players. Monocytes comprise 10% and 4% of human and mouse blood leukocytes, respectively. The main subset of CD115^{+} monocytes in mice express high levels of Ly-6c, CCR2 and CD62L and low level of CX_3CR_1[1]. Ly-6c^{high} monocytes are recruited to inflamed sites and produce high levels of pro-inflammatory cytokines, such as TNF-α and IL-1β. Hence, Ly-6c^{high} monocytes are named inflammatory monocytes. The second subset of mouse monocytes express a high level of CX_3CR_1 and a low level of Ly-6c. They reside in blood vessels in steady state and may play important roles in scavenging oxidized lipids, dead cells and pathogens[2]. Both monocyte subsets circulate in the blood and survey steady-state tissue by transporting self-antigens to lymph nodes with minimal differentiation to macrophages, but they can differentiate into macrophages and

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dendritic cells at sites of inflammation[3]. At least 3 subsets of monocytes exist in humans. $CD14^{++}$ $CD16^{-}$ monocytes resemble mouse Ly-$6c^{high}$ monocytes, $CD14^{++}$ $CD16^{+}$ monocytes have pro-inflammatory roles, and $CD14^{+}$ $CD16^{++}$ monocytes exhibit patrolling behavior similar to mouse Ly-$6c^{low}$ monocytes.

Macrophage origins

During embryonic development, various organs are seeded by macrophages derived from yolk sac or liver progenitors. Most of these macrophages can self-maintain by homeostatic proliferation[4,5]. Such self-maintenance was first investigated in microglia, which respond to various injuries, including CNS damage, and can self-renew without blood monocyte contribution[6]. Steffen Jung and his colleagues used constitutive and conditional CX_3CR_1 reporter mice to demonstrate that tissue-resident macrophages, including Kupffer cells and lung, splenic and peritoneal macrophages, are established before birth and can replenish themselves in adulthood by local proliferation[7]. These data were consistent with the findings by Geissmann and his colleagues[8], who described that the origin of yolk sac-derived tissue resident macrophages is independent of Myb, a transcription factor required for HSC and monocyte development. Taken together, these studies, in addition to others, indicate that many tissue resident macrophages are not derived from monocytes in steady state, at least in young mice. Two notable exceptions are dermal and intestinal macrophages. The dermis is populated by various myeloid cells, including macrophages and dendritic cells. Dermal macrophages are highly phagocytic but do not efficiently activate T cells, whereas dermal dendritic cells have strong T cell stimulatory capacity. In a recent study[9], Sandrine Henri and her colleagues found that, after 8 weeks of parabiosis, about 20% of dermal macrophages were parabiont-derived, indicating their monocytic origin. Intestinal macrophage maintenance also depends on blood monocytes[10,11]. A recent study[12] showed that although yolk sac and fetal macrophages seed the lamina propria, they begin to wane right after birth and are replaced by blood monocytes. This process depends on CCR2 and commensal gut microbiota; mice maintained in germ-free conditions have fewer colon macrophages than those in regular housing.

Like other organs, the heart contains macrophages in steady state[13,14]. A recently published study[15] characterized cardiac macrophage subsets and investigated their origins. The authors reported four cardiac macrophage subsets expressing varying levels of Ly-6c and MHC class II. Cardiac macrophages are derived from yolk sac and fetal monocyte progenitors and are replenished by local proliferation in steady state. Yet in injury, such as myocardial infarction, cardiac macrophages are replaced by blood monocytes[13]. Contrary to the notion that cardiac macrophages self-maintain by proliferation, a very recent study[16] demonstrated that embryonic-derived cardiac macrophages are continuously replenished by blood monocytes in adulthood. Almost all cardiac macrophages are $CX_3CR_1^{+}$ and MHC class II^{-} at birth; however, with age they diversify into four subpopulations with progressive increases in MHC class II^{+} and decreases in $CX_3CR_1^{+}$ subpopulations.

Monocyte production in steady state

Monocytes develop from bone marrow hematopoietic stem cells (HSC) after going through several progenitor stages, including common myeloid progenitor (CMP), granulocyte/macrophage progenitor (GMP) and macrophage/dendritic cells progenitor (MDP). Blood monocyte development depends on M-CSF[1,17]. M-CSF-deficient op/op mice have drastic reductions in blood monocyte numbers[18] and atherosclerotic plaque burden if crossbred with LDLR$^{-/-}$ mice[19]. M-CSF is also involved in tissue resident macrophage proliferation. Erlebacher and his colleagues[20] found that macrophage proliferation in the uterus during pregnancy was driven by M-CSF. Moreover, the proliferating macrophages produced higher levels of mcp-1, a CCR2 ligand in the myometrium, leading to extravasation of Ly-6c^{high} monocytes. Another example of M-CSF-dependent macrophage proliferation is that the cytokine induces Gata6-dependent peritoneal macrophage proliferation[21]. Additionally, M-CSF enhances tissue macrophage survival by reducing apoptosis[22].

Several transcription factors, such as PU.1, determine HSC differentiation into CMP rather than common lymphoid progenitors (CLP)[23]. PU.1 binds to GATA-1 and inhibits commitment towards a megakaryocyte-erythroid progenitor, which facilitates myeloid differentiation[24]. Moreover, PU.1 represses mast cell development. Other transcription factors, such as CCAAT/enhancer binding protein (Cebpa), early growth response gene and IFN consensus sequence binding protein[1,25–27], also determine myeloid vs. lymphoid lineage fate. Surprisingly, Cebpa expression in B and T lymphocytes can transdifferentiate them into macrophages[28,29]. Ikaros, a transcription factor that encodes a family of hematopoietic-specific zinc finger proteins, is a central regulator of lymphocyte differentiation.

Transcription factors involved in Ly-6c^{high} vs. Ly-6c^{low} monocyte generation are not well understood, with the exception of the orphan nuclear hormone receptor Nr4a1 (also known as Nur77), which is involved in Ly-6c^{low} monocyte production and survival[30]. However, some reports indicate that the transcription factor is dispensable for Ly-6c^{low} macrophage production[31].

Monocyte production after myocardial infarction

Myocardial infarction activates adrenergic signaling that alerts bone marrow niche cells, which reduce production of HSC retention factors[32] (Figure 1). Consequently, HSC egress from the bone marrow and seed in the spleen. This triggers extramedullary hematopoiesis and monocyte production. Within 24 hours after myocardial infarction, the spleen's monocyte reservoir is released[33]. Splenectomy experiments indicated that the organ may contribute as much as half of the monocyte population recruited to the infarct. Within four days after MI, the splenic monocyte reservoir refills by proliferation and differentiation of HSC and progenitors[34]. In the spleen, HSC proliferation is stem cell factor (SCF)-dependent. Neutralizing SCF reduces HSC proliferation and monocyte production[32]. Splenic monocyte production from hematopoietic progenitors also depends on IL-1β[34], IL-3 and GM-CSF[35]. Currently, mechanics of splenic HSC maintenance are mostly unknown. We recently found that macrophages are important players in splenic HSC retention, as

depleting splenic macrophages with M-CSFR knockdown or diphtheria toxin in CD169-DTR mice mobilized splenic HSC and reduced monocyte production[36]. Interestingly, splenic macrophages retain HSC via VCAM-1.

Monocyte release from hematopoietic organs in steady state and after MI

Monocyte release from the bone marrow follows the circadian rhythm, peaking at ZT4 and reaching nadir at ZT 16[37]. Blood monocytes' diurnal rhythm is linked to fluctuation of several clock genes, such as *Bmal1*, *Nrld1* and *Dbp*. Diurnal variation of monocyte egress from the bone marrow and increaed release during inflammaiton are driven by changing Mcp-1 levels in the blood. Listeria monocytogenes infection triggers higher blood monocyte levels and results in higher mortality due to massive 'cytokine storm'. Consistent with this, TLR9 expression on peritoneal macrophages followed a similar circadian rhythm, and vaccination using a TLR9 ligand when TLR9 expression is high improved the adaptive immune response[38].

Like monocyte fluctuation, mortality and morbidity after myocardial infarction also follow circadian rhythms. Disrupted diurnal levels aggravated myocardial remodeling and function following MI[39]. During the first 5 days after MI, a critical time for scar formation, there are high macrophage levels in the infarct. Homozygous clock mutant mice exhibited similarly aggravated ventricular remodeling after MI, which accords with the idea that blood monocyte levels, regulated by circadian rhythm, may determine myocardial repair post MI. This theory was also supported by a clinical study[40] reporting that infarct size peaked at 1:00 a.m. in patients with ST-segment elevation myocardial infarction.

Monocytes leave the bone marrow during diseases, such as infections, atherosclerosis and myocardial infarction. Monocyte release after LPS challenge was accompanied by elevated Mcp-1 production by mesenchymal stem cells and Cxcl12-abundant reticular cells lining bone marrow sinusoids. Conditional deletion of Mcp-1 from these cells significantly reduced monocyte egress after LPS challenge. In addition to mesenchymal stem cells, bone marrow endothelial cells may produce Mcp-1 after MI. Similar to monocyte release after LPS challenge, these cells can also produce Mcp-1, resulting in their mobilization into the blood. However, this hypothesis remains to be investigated. As mentioned above, the spleen functions as monocyte reservoir. After MI, monocyte departure from the splenic red pulp depends on angiotensin II-angiotensin 1 receptor signaling[33]. Angiotensin II infusion in mice reproduced MI-induced motility of splenic monocytes and their release into the blood[41].

Monocyte recruitment to the myocardium after MI

After myocardial infarction, circulating monocytes produced in the bone marrow and spleen are recruited to the infarct in two phases[42], with the first phase dominated by Ly-6c^{high} monocytes. Recruitment of Ly-6c^{high} monocytes is CCR2-dependent. Ccl2 and Ccl7, both ligands for CCR2, are expressed at high levels in infarcted myocardium[43,44]. B cells in ischemic myocardium are likely the source of Ccl7 after MI. Depleting B cells resulted in improved ventricular function accompanied by reduced monocyte recruitment[44]. In the second phase of post-MI monocyte response, Ly-6c^{low} monocyte recruitment depends on

Cx_3cr_1[42]. However, compared to the early recruitment of inflammatory monocytes, far fewer Ly6C^{low} monocytes are recruited to the infarct, and Ly6C^{high} monocytes can give rise to Ly6C^{low} macrophages in later healing stages[45]. Other mononuclear chemoattractants, such as Ccl-3 and Ccl4, are also highly expressed in infarcts[46], but their role in myocardial injury remains unstudied. Additionally, ELR-containing Cxc chemokines, which are strong neutrophil chemoattractants, are present in the infarct at high levels[47].

Monocyte/macrophage functions after myocardial infarction

The two sequential monocyte/macrophage phases are both important for healing after acute MI. Ly-6c^{high} monocytes give rise to early inflammatory macrophages, and both clear damaged tissue by phagocytosis and secreting proteolytic enzymes. In the second phase, Ly-6c^{low} macrophages facilitate wound healing and regeneration by promoting myofibroblast accumulation, collagen deposition and angiogenesis. Infiltrated monocytes may also interact with extracellular matrix in the damaged myocardium, leading to fibronectin release[48]. Fibronectin stabilizes the infarct and reduces infarct rupture. Once in the infarct, monocytes differentiate into macrophages in the presence of M-CSF. Macrophages promote angiogenesis, fibroblast proliferation and extracellular matrix deposition. Myofibroblasts, which are modified fibroblasts and α-smooth muscle actin-positive, are the major sources of collagen in the infarct. Myofibroblast differentiation is TGF-β-dependent. Macrophages also play a role in organ regeneration. Though myocardial infarction in adult mammals leads to scarring and diminished ventricular function, neonatal mouse hearts can regenerate after MI without scarring[49], but depleting cardiac macrophages impedes this repair process. A recent study[50] showed that embryonic-derived cardiac macrophages promote angiogenesis and healing after myocardial damage. Consistent with this, salamander limb regeneration also depends on macrophages[51]. While inflammation is required for cellular debris removal and new tissue formation after ischemic injury, exaggerated inflammation may impede the healing process, as shown in ApoE$^{-/-}$ mice with coronary ligation[52]. Accordingly, blood monocyte count after MI positively correlates with left ventricular end-diastolic volume and negatively correlates with ejection fraction in patients[53]. Mcp-1-deficient mice have markedly less monocyte recruitment to the infarct and, consequently, significantly fewer macrophages therein[43]. Even though Mcp-1-deficient and wild type mice had similar infarct sizes, the Mcp-1-deficient mice had improved ventricular function, thereby indicating monocytes' importance in myocardial healing after MI.

Conclusions

Monocytosis ensues during myocardial infarction and is vital to eradicating pathogens in systemic or local infection. However, since exaggerated monocytosis impairs healing, as discussed above, curbing monocyte recruitment to the infarct may improve ventricular function[54]. Additionally, MI-induced monocytosis exacerbates other cardiovascular complications. In a clinical study by Chen and his colleagues[55], patients with ST elevation MI had accelerated non-culprit coronary artery lesion atherosclerosis. Consistent with the finding in mice[32], patients with acute myocardial infarction had higher splenic metabolic activity as determined by whole body ^{18}F-FDG PET-CT[56]. Although the PET imaging agent

reports glucose uptake and is not cell-type specific, the data may indicate higher hemaotpoietic progenitor proliferation in the spleen after MI. By blocking the β3 adrenoreceptor, we decreased HSC egress from the bone marrow and thereby reduced monocytosis after MI in ApoE$^{-/-}$ mice[32]. Additionally, splenic HSC proliferation depends on stem cell factor (SCF), and SCF neutralization reduced extramedullary monocytosis after MI. Monocyte release from hematopoietic organs depends on angiotensin-II receptor signaling and CCR2 and could be a target for drug development. Following this line of inquiry, we found that CCR2 knockdown decreased inflammatory monocyte recruitment to the infarct, thereby facilitating the healing process[34,54]. Like monocyte production and migration, macrophage polarization may be harnessed to reduce complications of myocardial ischemia, especially heart failure[57].

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Abbreviations

MI	Myocardial infarction
HSC	Hematopoietic stem cells
GMP	Granulocyte macrophage progenitors
CLP	Common lymphoid progenitors
M-CSF	Macrophage colony stimulating factor

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Significance

Myocardial infarct is the leading cause of death in developed countries. The myocardium undergoes a rapid turnover after myocardial infarction, which is crucial for proper healing. Cells of myeloid origin, particularly monocytes, play a major role in the healing process.

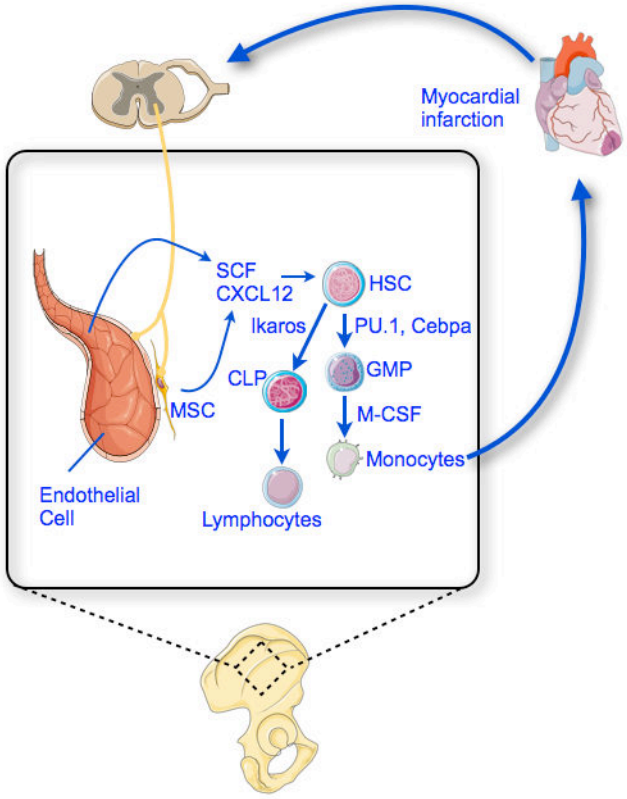

Figure 1. Monocytosis after myocardial infarction

Myocardial infarction activates sympathetic activity in the bone marrow. Consequently, HSC niche cells, such as mesenchymal stem cells (MSC) and endothelial cells, produce lower levels of HSC retention factors, like CXCL12. This leads to increased myeloid progenitor proliferation and differentiation into monocytes. Newly made monocytes are released from the bone marrow and spleen and then recruited to the infarct via blood.