Macrophages are innate immune cells that pursue a plethora of functions in steady state and disease. The name big eater refers to their uptake of invading pathogens, dying cells, foreign bodies, and other materials, including cholesterol. The macrophage phenotype and their tissue-specific functions depend on the environment in which they reside. For instance, macrophages may contribute to the regulation of thermogenesis, influence the electrolyte balance or iron recycling.\(^1\) Fate-mapping studies revealed a dichotomy for macrophages’ sources: contrary to previous dogma, tissue-resident macrophages in the brain, liver, lung, and skin do not derive from monocytes that circulate in the blood but are replenished through local proliferation.\(^2\)-\(^5\) Tissue-resident macrophages in the intestine and inflammatory macrophages in sites of acute inflammation, however, derive from monocytes that were produced in the bone marrow or in the spleen.\(^6\)\(^7\)

Recently, it emerged that macrophages populate the healthy and diseased myocardium. Although their higher numbers and

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**Rationale:** Macrophages populate the steady-state myocardium. Previously, all macrophages were thought to arise from monocytes; however, it emerged that, in several organs, tissue-resident macrophages may self-maintain through local proliferation.

**Objective:** Our aim was to study the contribution of monocytes to cardiac-resident macrophages in steady state, after macrophage depletion in CD11b\(^{DTR/-}\) mice and in myocardial infarction.

**Methods and Results:** Using in vivo fate mapping and flow cytometry, we estimated that during steady state the heart macrophage population turns over in \(\approx 1\) month. To explore the source of cardiac-resident macrophages, we joined the circulation of mice using parabiosis. After 6 weeks, we observed blood monocyte chimerism of 35.3\(\pm\)3.4\%, whereas heart macrophages showed a much lower chimerism of 2.7\(\pm\)0.5\% \((P<0.01)\). Macrophages self-renewed locally through proliferation: 2.1\(\pm\)0.3\% incorporated bromodeoxyuridine 2 hours after a single injection, and 13.7\(\pm\)1.4\% heart macrophages stained positive for the cell cycle marker Ki-67. The cells likely participate in defense against infection, because we found them to ingest fluorescently labeled bacteria. In ischemic myocardium, we observed that tissue-resident macrophages died locally, whereas some also migrated to hematopoietic organs. If the steady state was perturbed by coronary ligation or diphtheria toxin–induced macrophage depletion in CD11b\(^{DTR/-}\) mice, blood monocytes replenished heart macrophages. However, in the chronic phase after myocardial infarction, macrophages residing in the infarct were again independent from the blood monocyte pool, returning to the steady-state situation.

**Conclusions:** In this study, we show differential contribution of monocytes to heart macrophages during steady state, after macrophage depletion or in the acute and chronic phase after myocardial infarction. We found that macrophages participate in the immunosurveillance of myocardial tissue. These data correspond with previous studies on tissue-resident macrophages and raise important questions on the fate and function of macrophages during the development of heart failure. \((\text{Circ Res. 2014;115:284-295.})\)

**Key Words:** heart ■ macrophages ■ monocytes ■ myocardial infarction
density rendered them an easy-to-discern and well-studied cell population in acutely ischemic heart tissue, their interspersed position in between myocytes, fibroblasts, and endothelial cells in the steady-state myocardium was a likely reason why the cells previously escaped detection. The advent of more sensitive imaging tools and genetic reporter proteins, together with methods to detect even sparse leukocyte populations in tissue by flow cytometry, leads to an increased appreciation of macrophages' presence in healthy and also in chronically diseased myocardium. Given the recent description of macrophages in the murine myocardium, we are just beginning to understand the cells' functions in the steady-state heart and in heart failure. For other organs, there is a rich body of knowledge on macrophages' role in health and disease, indicating that these cells promote tissue destruction, fibrosis, angiogenesis, and instruct local tissue progenitors.

Here we investigated the maintenance of cardiac-resident macrophages by assessing cell turnover as well as the contribution of bone marrow–derived monocytes to the pool of heart macrophages in steady state and disease. Steady-state heart macrophages proliferate locally and self-renew independently of circulating monocytes. However, monocytes contribute to macrophages in the acute infarct or after induction of macrophage death in CD11bDTR/+ mice.

Methods

Animals and Procedures

All experimental animal procedures were performed according to the Subcommittees on Animal Research Care at Massachusetts General Hospital. All experiments were performed with 10- to 12-week-old female animals. C57BL/6J (stock 000664), hemizygous B6.129P-30Scha/J (stock 004353), and B6.SJL-αSMARFP mice were a kind gift from David Brenner. Mice C57BL/6-JBoyJ mice (stock 001280), Cx3cr1tm1Litt/J (cx3cr1 GFP/+; stock 005582), B6.FVB-Tg (ITGAM-IL7Rα)low c-kithigh Sca-1high CD48neg CD150high obtained from CD45.2+ were joined by parabiosis using either CD45.2- and green fluorescent protein (GFP)-expressing males and CD45.2- and red fluorescent protein (GFP)-expressing females. Antibodies were purchased from eBioscience, Biolegend, or BD Biosciences. Monocytes were identified as Lineage (CD90/CD19/Ki-67)/Ly-6Chigh CD11b+ F4/80+ CD11c+ Ly-6C/r+ and, Ly-6C/r+ high. Macrophages were identified as Lineage (CD90/CD19/Ki-67)/Ly-6G/Gr1+ CD11b+ F4/80+ high, CD11c+ Ly-6C/r+ high. Monocytes were identified as lineage (CD90/CD19/CD11b+ Ly-6G/Gr1+ and, Ly-6C/r+ high). Bone marrow transplantation for adoptive transfer experiments, recipient GFP mice were lethally irradiated (10 Gy) and transplanted intravenously with 100 FACS-sorted hematopoietic stem cells (SLAM HSC) defined as Lineage (CD90/CD19/CD45.2)/Low c-kithigh Sca-1high CD48neg CD150high obtained from CD45.2+ mice.

In Vivo Phagocytosis Assay

C57BL/6 mice received 4 injections (10 μg each) of pHrodo Green Staphylococcus aureus (2 mg/mL; Life Technologies) into the left ventricular myocardium 2 hours before euthanization. Green fluorescence of injected bacteria is only induced on phagocytosis and contact to low pH in phagosomes. Uptake in target cells was assessed directly before FACS analysis. Data were acquired on an LSRII (BD Biosciences) and analyzed with FlowJo software (Tree Star).

Cell Tracking

Vybrant diododecyldimethylamino benzene-carboxylic acid (DiD) cell-labeling solution (Molecular Probes) was diluted 1:100 in PBS, and 10 μL was injected at 5 different spots into the myocardium before myocardial infarction (MI) was induced by coronary ligation. Injected mice were then analyzed for DiD fluorescence at 24 hours and evaluated for cardiac function.

Immunofluorescence Microscopy

Hearts were harvested, flushed with 0.9% saline buffer, fixed in 4% paraformaldehyde (methanol-free; Electron Microscopy Science) for 3 hours, and immersed in 30% sucrose in PBS overnight. Then tissue was embedded in Tissue-Tek OCT compound (Sakura Finetek) and frozen in an isopentane bath on dry ice.
Figure 1. Resident cardiac macrophages in the healthy heart. A, Gating strategy for identification of CD45− nonleukocyte cells, lymphocytes (identified as CD45+, CD11b−, and SSC−), and heart macrophages (identified as CD45high F4/80high Ly6Clow) by flow cytometry. Frequencies within the entire heart are provided as mean±SEM. B, Green fluorescent protein (GFP) expression in Cx3cr1GFP/+/− mice in different cell types, compared with C57BL/6 mice. C, Immunofluorescence microscopy of healthy heart tissue showing costaining of MAC3 or F4/80 (D) with nuclear staining (DAPI) and the Cx3cr1GFP/− reporter (right). E, Immunofluorescence microscopy of healthy myocardium in a Cx3cr1GFP/− αSMA−/− dual-reporter mouse. F, Immunofluorescence microscopy of healthy myocardium in a Cx3cr1GFP/− reporter mouse stained for the fibroblast reporter DDR2. G, Immunohistochemical staining for CD68 in human myocardium. H, Cytospin preparation of FACS-isolated macrophages shows typical macrophage morphology. Scale bars indicate 5 μm.
staining, 25-μm sections were stained with anti-MAC3 antibody (clone M3/84; BD Biosciences) followed by a biotinylated anti-tet secondary antibody and streptavidin-DyLight 594 (Vector Laboratories, Inc). Fluorescent terminal deoxynucleotidyl transferase dUTP nick-end labeling staining was performed using DeadEnd Fluorometric terminal deoxynucleotidyl transferase dUTP nick-end labeling system (Promega), and fibroblasts in heart were detected using DDR2 antibody (LifeSpan BioSciences, Inc). The sections were counterstained with DAPI (Life Technologies) to identify nuclei. Images were captured using a Nikon Eclipse 80i (Nikon Instruments, Japan), or slides were scanned with NanoZoomer 2.0-20RS in high-resolution mode (Hamamatsu, Japan).

Human Myocardial Histology
Postmortem tissue specimens of the left ventricle were collected from 5 patients who were referred to the Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands, for clinical autopsy (n=5; 3 men; age, 58±20 years). All 5 patients died from a cause not related to cardiac disease (acute aortic rupture/dissection, n=3; chronic obstructive pulmonary disease, n=1; trauma, n=1). Tissue specimens were formalin-fixed and paraffin-embedded.

Statistics
Data are expressed as mean±SEM. Analyses were performed using Prism 6.0a (GraphPad Software Inc). For a 2-group comparison, a Student t test was applied if the pretest for normality (D’Agostino–Pearson normality test) was not rejected at 0.05 significance level; otherwise a Mann–Whitney test for nonparametric data was used. ANOVA tests followed by Bonferroni post-tests were applied for comparison of >2 groups. P values <0.05 indicate statistical significance.

Results
Resident Heart Macrophage Turnover Is Slow During Steady State
Using flow cytometry, we estimated that leukocytes contribute 10.3±0.4% of all murine cardiac cells and that CD45+ CD11b+ F4/80+ Ly6C− macrophages are the most prominent population among cardiac leukocytes (7.9±0.3% of all cardiac cells; Figure 1A). Previously, the Rosenthal group visualized cardiac-resident macrophages in the healthy myocardium using fractalkine Cx3cr1GFP reporter mouse. Because the fractalkine receptor may be expressed by various cell types, we investigated Cx3cr1GFP reporter expression by CD45+ cells (CD45+ cells include fibroblasts, endothelial cells, and myocytes), lymphocytes, and macrophages. We confirmed that Cx3cr1GFP is expressed by macrophages in the healthy murine heart, whereas other cardiac cells, including CD45+ fibroblasts, do not show Cx3cr1 expression by FACS (Figure 1B). In addition, GFP+ cells in Cx3cr1GFP mouse expressed MAC3 (Figure 1C) and F/80 (Figure 1D) on multicolor fluorescence histology. Because heart macrophages’ spindle-like shape resembles fibroblasts, we crossed Cx3cr1GFP+ mouse with a αSMA−/− mouse strain in which myofibroblasts are red. These dual reporter mice showed green and red protein reporter expression in different cells on fluorescence microscopy (Figure 1E), clearly separating Cx3cr1GFP+ macrophages from myofibroblasts. We further stained myocardium from Cx3cr1GFP+ mice for the fibroblast marker DDR2 and likewise did not find colocalization of GFP macrophage signal with fibroblasts (Figure 1F). In a series of 5 autopsy cases, we stained human left ventricular myocardial tissue for the macrophage marker CD68. Macrophages were found in all examined human hearts. Depending on the orientation of myocardial fibers in the section, we observed similar spindle-like macrophage shapes in human myocardium (Figure 1G). Finally, we FACs-sorted GFP+ cells from 2 Cx3cr1GFP hearts for a cytospin preparation. When placed on a microscopy slide, GFP+ cells assumed the typical irregular round shape of macrophages (Figure 1H).

To explore the turnover kinetics of cardiac-resident macrophages, we performed a pulse-chase experiment with BrdU. After loading heart macrophages with BrdU by daily injections for 4 weeks (wash-in phase; pulse), saturation was measured in a first cohort. A similarly treated littermate cohort was assessed after an additional 3-week wash-out (chase) without further BrdU exposure. We found that the BrdU label in heart macrophages decreased from 40.1±1.4% at the end of the pulse phase to 15.5±2.0% at the end of the chase phase, reflecting cell turnover (Figure 2). This 2.6-fold decrease of BrdU-positive macrophages within 3 weeks indicates that cardiac-resident macrophages turn over slowly in steady state. Extending on the 2.6-fold decrease of BrdU-positive macrophages in 3 weeks, one can extrapolate that it would take 2 additional weeks until all BrdU-positive cells...
were lost, and hence the entire macrophage population had turned over. We also measured BrdU kinetics in lung and spleen macrophages in the same mice. Here we found a decrease of BrdU-positive macrophages from 34.4±2.4% after wash-in to 16.1±0.6% after wash-out in the lung and from 6.7±1.1% to 3.3±0.5% in the spleen. These data are in the range of previously reported values,5 thus validating our experimental set-up.

Monocytes Contribute Sparingly to Resident Heart Macrophages in Steady State
To answer the question whether circulating monocytes contribute to the turnover of heart macrophages, we investigated heart macrophage chimerism after putting C57BL/6 CD45.2+ and CD45.1 mice in parabiosis for 6 weeks. During parabiosis, the circulation of 2 mice links, and circulating cells, including monocytes, mix in the blood of both parabionts. After 6 weeks of parabiosis, the blood chimerism for Ly6C^high and Ly6C^low monocytes was 22.8±1.1% and 35.3±3.7%, respectively. The chimerism of resident heart macrophages was much lower at 2.7±0.5% (Figure 3A and 3B).

Although parabiosis provides a convenient tool to study recruitment of cells, it may induce artifacts through pro-inflammatory stimuli. Therefore, to study recruitment in a separate experiment, we adoptively transferred bone marrow...
hematopoietic stem cells into irradiated recipient mice to (1) investigate whether monocytes give rise to heart macrophages for a longer period of time, and (2) to enforce higher monocyte blood chimerism than what can be achieved by parabiosis. Recipient ubiquitous GFP+ mice were irradiated (950 cGy) and transplanted with 100 SLAM HSC harvested from non-GFP CD45.2+ mice. Additionally, we cotransferred GFP+-supportive bone marrow cells, which have a limited life span and served the purpose to bridge the recipients’ hematopoietic system until the transferred stem cells expand to sustain hematopoiesis and to respond to any acute radiation-induced heart injury. Eighteen weeks later, we measured the percentage of topoiesis and to respond to any acute radiation-induced heart injury. To assess local proliferation as the source for cell turn-over of resident heart macrophages, we used a 2-pronged approach. First, mice received 1 injection of BrdU, followed by flow cytometric analysis of heart macrophages 2 hours later. We found BrdU-positive monocytes in the bone marrow, but they did not yet egress into the blood pool within this short 2-hour time window (Figure 3D). We found that 2.1±0.3% of heart macrophages stained positive for the BrdU label (Figure 3D).

Cardiac-Resident Macrophages Phagocytose Pathogens
To assess whether heart macrophages are involved in host defense against pathogens that may enter the myocardium, we injected fluorescent S. aureus into the left ventricular myocardium. The fluorescence of the probe is only detectable if the bioparticle is activated by exposure to low pH in lysosomes, indicating phagocytosis. We detected fluorescence in 11.4±1.2% of heart macrophages 2 hours after injection of bacteria (Figure 4). These data indicate that macrophages participate in immunosurveillance of the heart.

Monocytes Repopulate Depleted Heart Macrophages
We next explored whether monocytes contribute to the replenishment of cardiac macrophages after their depletion in CD11bDTR+ mice. To this end, we injected mice with a single dose of diptheria toxin, thus inducing apoptosis of CD11b+ mononuclear cells in this transgenic mouse. The recovery of blood monocytes and heart macrophages was then monitored by flow cytometry for several days. Ablation of CD11b+ cells drastically reduced the number of circulating monocytes and heart macrophages (Figure 5A–5C). After 3 days, monocytes reappeared in the blood and also invaded the heart, whereas heart macrophages were still absent. Six days after ablation, the macrophage population recovered (Figure 5A–5C).

To investigate whether this recovery was caused by differentiation of recruited monocytes, we studied macrophage recovery in CD11bDTR+/UbcGFP parabionts. Two weeks after parabiosis, CD11b+ cells were depleted in the CD11bDTR+ parabiont by injection of diptheria toxin, whereas GFP+ donor monocytes of the coparabiont remained in circulation. On day 6 after depletion, the chimerism for heart macrophages resembled the monocyte chimerism in the blood (Figure 5D). These data indicate that monocytes repopulate the cardiac macrophage pool after myeloid cell depletion in CD11bDTR+ mice.

Monocytes Give Rise to Infarct Macrophages
We next studied the monocyte and macrophage population in mice with coronary ligation, a clinically relevant cardiac injury model. Interestingly, resident heart macrophages were completely lost in 24-hour-old infarcts (Figure 6A), whereas inflammatory monocytes were entering the infarcted tissue. This observation is unlikely caused by phenotypic cell changes or downregulation of macrophage markers after ischemia because we used a combination of several leukocyte surface antigens for their detection. Four days after coronary ligation, the macrophage population recovered (Figure 6A).

The observed time course suggested that after ischemia, infarct-resident macrophages arise from monocytes. We directly tested this hypothesis in parabionts with coronary ligation using 2 different experimental timelines. First, we induced MI in C57BL/6 CD45.2+ mice after these had been in parabiosis with donor GFP+ mice for 2 weeks before coronary ligation. Parabiosis continued after MI. On day 4 after MI, the macrophage chimerism in infarct tissue was similar to the monocyte chimerism in blood, indicating that infarct macrophages derived from recruited cells. Even 4 weeks later, we observed a preserved elevated macrophage chimerism...
Figure 5. Monocytes contribute to macrophage recovery after induction of macrophage apoptosis. CD11b<sup>DTR+</sup> mice were injected with a single dose of diphtheria toxin (DT; n=3 per time point). FACS plots show depletion and recovery in blood (A) and the heart (B). C, Percentages of F4/80<sup>high</sup> Ly6C<sup>high</sup> monocytes and F4/80<sup>low</sup> Ly6C<sup>low</sup> macrophages in the heart after 1 DT injection, gated on CD45<sup>+</sup> Lineage<sup>−</sup> CD11b<sup>+</sup> cells. D, Macrophages were depleted in CD11b<sup>DTR+</sup> mice 2 wk after establishing parabiosis with UbcGFP<sup>+</sup> mice. Percentages of donor green fluorescent protein (GFP)-positive cells in peripheral blood monocytes and cardiac macrophages were assessed in parabionts after 6 d (n=4).
in the infarct (Figure 6B). Second, we put mice in parabiosis 2 weeks after coronary ligation. Chimerism was measured 4 and 16 weeks later. Interestingly, this alternative timing resulted in lower infarct macrophage chimerism (Figure 6C), indicating that after the acute phase of monocyte recruitment in the first 2 weeks after MI, the infarct macrophage resident population regains independence from the monocyte blood pool and instead again relies on proliferation as observed in the steady state.

**Macrophages in Acutely Ischemic Myocardium Die Locally and May Emigrate**

To explore the mechanism of macrophage reduction in acutely ischemic myocardium, we investigated whether cardiac-resident macrophages undergo local cell death similar to ischemic myocytes. Indeed, 12 hours after coronary ligation, we found a significantly increased rate of TUNEL+ MAC3+ cells, whereas double-positive cells were rarely observed in parabionts 4 d (n=6 pairs) and 1 mo after MI (n=5 pairs). C, C57BL/6 CD45.2+ and UbcGFP+ mice were put in parabiosis 2 wk after MI. Percentages of GFP+ cells among peripheral blood monocytes and heart macrophages were assessed in parabionts after 4 (n=8) and 16 wk (n=4; mean±SEM; **P<0.01 vs blood Ly6Chigh monocytes).
We had previously observed that infarct macrophages may exit the heart at low numbers. We, therefore, investigated whether cardiac macrophages that reside in the myocardium before coronary artery ligation may exit the acutely ischemic myocardium. To test for macrophage exit, we had to preferentially label cardiac cells but not tissue-resident macrophages in likely destination organs. To this end, we stained myocardium in vivo with DiO. This procedure labeled 12% to 16% of cardiac-resident macrophages (Figure 8) but failed to stain bone marrow monocytes (Figure 8G), suggesting that the myocardial dye injection did not cause unspecific myeloid cell staining in the bone marrow. We next explored whether the observed disappearance of macrophages after coronary ligation still occurs after intramyocardial dye injection. This was the case, because DiO+ macrophages disappeared at similar rates as observed in mice that did not undergo the labeling procedure (Figure 8C). Thus, we injected the dye into the myocardium of 8 mice, 4 of which consecutively underwent coronary ligation. Twenty-four hours later, we examined the mediastinal lymph node, the spleen, and the bone marrow by FACS. Ischemia did not change the presence of DiO+ macrophages in the mediastinal lymph node (Figure 8D); however, the percentage of DiO+ macrophages doubled in the spleen and bone marrow of mice that were subjected to myocardial ischemia (Figure 8E and 8F).

**Discussion**

Although the role of macrophages in cardiovascular disease is well understood, it was only recently noted that there is a sizable tissue-resident macrophage population in the normal myocardium at all times. Macrophages were also described in human myocardium by immunoreactive staining, albeit at lower numbers. In contrast to detailed reports on tissue-resident macrophages in other organs, the origin and maintenance of cardiac-resident macrophages remained unclear until recently. While our article was in revision, the origins of steady-state cardiac macrophages were described for the first time. The cells arise from embryonic yolk-sac progenitors before birth and self-maintain independent of bone marrow–derived monocytes. The results presented here independently confirm that local proliferation dominates supply of local macrophages in the healthy myocardium, as we also found a minimal contribution of blood monocytes to steady-state cardiac-resident macrophages.

When the steady state was perturbed, macrophages mostly derived from blood monocytes. After induction of macrophage apoptosis in CD11b\textsuperscript{DTR+} mice, monocytes replenished the cardiac macrophage pool. These results correlate well with the observations after clodronate liposome macrophage depletion. Although macrophages residing in acute infarcts may also proliferate, we found that they overwhelmingly derive from circulating monocytes. These cells are recruited at high levels during the first 2 weeks after ischemia. If parabiosis was induced 2 weeks after MI, infarct macrophages did not depend on monocyte supply any longer.

Interestingly, we observed a sudden, almost complete disappearance of heart macrophages in the first 24 hours after ischemia in the infarct. Our histological and FACS data suggest that local cell death, akin to the demise of ischemic myocytes, is a dominant factor in this vanishing
As soon as 2 hours after ischemia, the number of dead macrophages significantly increased. We also detected an increased number of DiO+ macrophages in hematopoietic organs when this cell dye was delivered to the myocardium shortly before coronary artery ligation. It is currently unclear whether these DiO+ macrophages actively departed from the ischemic wound, and what the biological significance of this migration may entail. We speculate that these cells could be involved in the transfer of danger signals to remote locations.

We currently know very little about cardiac macrophages, which intermingle closely with myocytes, endothelial cells,
and fibroblasts in the steady state. The cells have a peculiar spindle-like shape and thus resemble fibroblasts. When viewed together with previous gene expression analyses,9,10 our histological studies make it unlikely that we confuse these 2 cardiac resident macrophages. The human autopsy data likewise show a spindle shape of CD68+ cells. This macrophage-unlike appearance may be caused by the structure of the cardiac tissue. The longitudinal orientation of myocardial fibers possibly dictates the spindle-like macrophage appearance. In day-old infarcts, where the typical longitudinal myocardial structure is lost, macrophages, including GFP+ macrophages in the Cx3cr1GFP/+ reporter mouse, appear as round cells with dendrites,18 supporting the argument that the tissue environment may form macrophage shapes.

The translational implications of cardiac-resident macrophages are foreshadowed by the important tasks of their counterparts in other tissues, where macrophages regulate bone matrix turnover, dictate the micromilieu for progenitor and stem cells, instruct the metabolism of resident adipocytes, and pursue sentinel functions against invading pathogens.12 Future work will investigate cardiac-specific tasks of macrophages. Data presented here indicate that the cells participate in immunosurveillance and may support host defense against pathogens in the heart. Thus, macrophages or their compromised function may be relevant in endocarditis, which is increasingly observed after invasive procedures.19,20

A recent report described 4 subsets of F4/80/MerTK+ resident macrophages with different expression of surface markers Ly6C+, major histocompatibility complex class II, and autofluorescence.10 It remains to be elucidated whether these macrophage subsets pursue distinct functions. It is clear, however, that a precise understanding of their tasks is a prerequisite for therapeutic targeting of these cells. Overabundance of inflammatory macrophages in the infarct compromises repair and promotes heart failure,9 rendering these cells a potential drug target. The selective monocyte contribution to infarct macrophages may thus offer the opportunity to target infarct macrophages via interfering with monocyte recruitment, for instance with in vivo RNAi,21 while sparing resident macrophages in the nonischemic myocardium.

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Disclosures

None.

References


## Novelty and Significance

**What Is Known?**
- Macrophages are innate immune cells residing in most tissues, including the steady-state myocardium and the acutely infarcted heart.
- Many inflammatory macrophages derive from circulating monocytes, whereas some resident macrophages, for instance in the brain or lung, do not.

**What New Information Does This Article Contribute?**
- In the steady state, cardiac-resident macrophages mostly derive from local proliferation and self-maintain independently of circulating monocytes.
- In contrast, bone marrow-derived monocytes give rise to macrophages in acute infarcts and after depletion.
- Cardiac-resident macrophages participate in immune surveillance.

Macrophages are frequent innate immune cells with important general and specialized functions in all major organs. For instance, macrophages provide a first line of defense in wound healing and against infection. However, the cells also give rise to pathology, including in atherosclerotic plaque and after myocardial infarction. Thus, they represent emerging therapeutic targets that have to be addressed with utmost care to avoid collateral damage. Recent data suggest that there are numerous cardiac macrophages in healthy and diseased hearts; however, their supply, a potential therapeutic target, was incompletely understood. The data presented here suggest a dichotomy: macrophages in healthy myocardium derive from local proliferation, whereas injury to the heart triggers a monocyte influx. These monocytes then differentiate into macrophages, suggesting that targeting cell recruitment or production in hematopoietic tissues is a potential therapeutic strategy to reduce inflammation in the heart without compromising resident macrophages. In addition, we report that cardiac macrophages react to myocardial ischemia with tissue exit and, dominantly, local death.
Differential Contribution of Monocytes to Heart Macrophages in Steady-State and After Myocardial Infarction

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The author name “Anja M. van der Laan” was misspelled as “van der Lahn”.

The error has been corrected in the online version of the article, which is available at http://circres.ahajournals.org/content/115/2/284.