Heart failure remains a critical target to improve the health of the US population. It is a major cause of morbidity and mortality in the United States. Heart failure is a result of acute or chronic injury followed by healing and remodeling that are insufficient to maintain or restore function. Myocardial infarction (MI) is the major cause of heart dysfunction, but other more chronic injuries, such as those caused by hypertension or genetic defects have many similarities.

The response to injury in MI can be parsed into multiple overlapping phases (Figure 1). The initial phase involves an acute inflammatory response and includes recruitment of inflammatory cells and the clearance of dead tissue. A subsequent phase involves the initial reparative response replacing the lost tissue and includes immune cells that will both terminate the initial inflammatory response and begin repair. This repair is followed by a more prolonged phase of continued remodeling that involves both destruction and replacement of tissue. Remodeling is sensitive to the presence of continued stress, which can have adverse consequences. The innate immune system has recently been shown to be important in cardiac response to MI. However, a role for adaptive immunity responding to damage has also been suspected with protection from MI. The response to injury in MI can be parsed into multiple overlapping phases (Figure 1).

Two recent studies show that both dendritic cells (DCs) and T cells are required for proper cardiac remodeling after MI and can play a beneficial role. These 2 studies have remarkably similar phenotypes. Although neither altered the infarct size, both altered the initial healing and remodeling responses. Both had decreased mature collagen fibers and angiogenesis. Both had some data for increased matrix metalloproteinases, which could affect remodeling. In particular, 2 of the 4 models with alteration of T-cell responses had decreased survival with increased cardiac rupture. A third model had increased left ventricular dilation. CD11c+ cell ablation also may have had an effect on survival although it was not statistically significant at the P<0.05 level. Most of the deaths were within the first week, suggesting that the initial healing response was compromised (summarized in Figure 1).

Anzai et al5 set out to determine whether DCs are important in MI. DCs are antigen-presenting cells that stimulate T cells, which in turn are major producers of cytokines, which can alter function of tissue parenchymal cell, macrophages, and other T cells (Figure 2). Anzai et al took the approach of using mice carrying a transgene of the diphtheria toxin (DT) receptor (DTR) driven by the CD-11c/Itgax promoter. Treatment with DT in these mice ablates nearly all CD11c+ cells, and mice carrying this transgene that are treated with DT have decreased survival. Bone marrow transplantation in which the donor carries the transgene restricts the destruction of CD11c+ cells to the bone marrow–derived compartments that turn over quickly. Therefore, more slowly replaced cell populations will not be eliminated with DT treatment, and survival is improved.

The identity of CD11c+ cells remains controversial. While in bone marrow, DCs express high levels of CD11c, and this correlates with major histocompatibility complex II (MHCII) expression and functional antigen presentation. However, outside the bone marrow, CD11c is not thought to be sufficient to identify DCs. Furthermore, it is not clear how robust the expression of the transgene needs to be to provide killing by the DT. Although DCs can lack CD11b, these researchers show that most of the CD11c+ cells infiltrating the heart are CD11b+ and MHCII+, indicating that these are myeloid DCs.

Anzai et al demonstrate that depletion of CD11c+ cells derived from a bone marrow transplantation is important in regulating the inflammatory response and monocyte/macrophage populations after acute MI. The result is not a change in infarct size but a thinner infarct wall with more immature collagen fibers. These differences have the potential to alter the strength of the infarct, which is a risk for rupture and carries a high mortality.

These results show how important a subpopulation of myeloid cells can be and illustrate how different cell types can be interdependent. They suggest that a critical feature of the important changes is the decrease in the Ly-6CLO and/or CD206+ population and the relative increase in the Ly-6CLO or CD206+ population. Ly-6C has previously been a marker that defines initial inflammatory cells followed by a population that promotes healing. CD206 similarly has been used to define macrophage subpopulations that have been called by different names, including alternatively activated macrophages or M2 (based on the ability of Th2 cytokines to induce CD206+ populations) and classically activated macrophages or M1 (induced by Th1 cytokines such as interferon-γ and activators of...
Toll-like receptor-4). The alternatively activated macrophage population in particular is highly heterogeneous and has been implicated in healing and fibrosis. Manipulation of the ratio of alternatively activated macrophage and classically activated macrophage populations has been implicated in cardiac remodeling in other cardiovascular injury models and recently as a mechanism for some of the beneficial cardiac effects of mineralocorticoid antagonists acting through myeloid cells. One of the problems is that the degree of inflammation can also influence the degree of healing required, so that the specific critical changes required have yet to be defined. Interestingly, in this model, as far as characterized, there appears to be a decrease in the alternatively activated macrophage population. The increase in the classically activated macrophage population may be a more direct effect or could arise from the decreased anti-inflammatory properties of the alternatively activated macrophage population, leading to a more persistent inflammation.

These results contrast with past results from eliminating CD11c<sup>+</sup> cells in inflammatory models of obesity. Previous researchers used the same methodology of bone marrow transplantation in CD11c-DTR animals treated with DT. The CD11c<sup>+</sup> cells in adipose tissue are highly proinflammatory, so their elimination led to less inflammation and abrogation of obesity-induced insulin resistance. This may point to markedly different subpopulations of CD11c<sup>+</sup> cells or to differences in function of different tissues.

Dovetailing with the study on DCs, in this issue, the study by Hofmann et al shows 2 important findings. First, they identify the cardiac draining lymph nodes in the mediastinum and show the effects of antigen-presenting cells resulting in an increase in T-cell Foxp3<sup>+</sup> cells (a marker for regulatory T cells) after an infarct. Second, they show the function of T cells in beneficial collagen formation and survival after infarction by disrupting T-cell function. To disrupt the T-cell function, they first used knockout of CD4, which prevents the formation of this functional subset of T cells. After infarction, the animals had increased left ventricular dilation, decreased infarct collagen density, and like the CD11c-DTR animals, increased inflammation and inflammatory monocytes. In the infarct, there was increased monocyte chemoattractant protein-1, an inflammatory cytokine, and matrix metalloproteinase-9 in CD11b<sup>+</sup> cells, although total collagenase activity in the infarct was unchanged.

A second transgenic model that has restriction of the T-cell responses (OT-II) showed a stronger phenotype with decreased survival after heart failure and increased cardiac rupture. The OT-II model did not display any changes in neutrophil or monocyte/macrophage numbers, suggesting that these innate immune cells were not mediating the

---

**Figure 1.** Phases of inflammation and healing after myocardial infarction and their alteration in transgenic models. The response to injury can be parsed into 3 phases: injury and inflammation, initial repair, and remodeling. Inflammation has associated proinflammatory leukocytes characterized by Ly-6C<sup>+</sup> monocytes or classically activated macrophages (CAM; which would be CD206<sup>+</sup>). Healing myeloid cells include Ly-6C<sup>lo</sup> and alternatively activated macrophages (AAM; CD206<sup>+</sup>). Both monocytes and macrophages are active in the first week. Anzai et al showed that CD11c<sup>+</sup> cells peak at ~1 week and include the myeloid dendritic cells. T cells measured by the general marker CD3 have a slightly longer time course. The changes seen in these models are shown. KO indicates knockout; MHCII, major histocompatibility complex class II; MMP, matrix metalloproteinase; IL, interleukin; and MCP, monocyte chemoattractant protein. *Primary defects.
Figure 2. Schematic of pathway from formation of cardiac debris containing antigens, processing by dendritic cells to display antigens, interaction with naive CD4+ T cells to produce proliferation, and differentiation to cell CD4+ cell types. Treg indicates regulatory T cells; MHCII, major histocompatibility complex class II; and TCR, T-cell receptor.

The innate immune cells have yet to be performed. A functional changes. However, full functional characterization of the innate immune cells has yet to be performed. A third model with ablation of the MHCII that would disrupt all T-cell activation with the MHCII, including CD4+ cell differentiation and activation, also had decreased survival similar to that of the OT-II model and had decreased collagen density.

So, are these 2 reports describing a direct pathway where the myeloid DC is the antigen-presenting cell to activate CD4 T cells (possibly regulatory T cells), leading to proper cardiac remodeling? Although enticing and even likely, the complexity and the lack of demonstrated direct connection between the models preclude concluding that this is the major mechanism. In addition, the differences in phenotype are not currently explained. The only information we have from DC ablation is that the total number of T cells is not changed in the time course after infarct, but we have no information on T-cell subtypes. Similarly, although the OT-II model does not have the changes in monocytes seen in both the CD11c-DTR and the CD4 knockout model, we do not know about function or even other myeloid cells such as macrophages or neutrophils. In particular, we do not have complete information about the cytokine, macrophage polarization, or other functions in the OT-II model to identify the critical changes that ultimately lead to deficient remodeling. By sorting these issues out, we can obtain a better delineation of the pathway and likely identify multiple steps that can be targeted therapeutically. However, given the tight interaction of the immune cells, rather than a linear pathway, we may find a system that is interdependent with multiple feedback arcs. These models all altered collagen. How these changes influence the type of collagen may also have profound effects on outcome. A recent report shows that the specific type of collagen can markedly influence outcome after MI. Therefore, further detailed analysis of extracellular matrix differences may be revealing.

These reports show models that had a less desirable outcome. Of course, the therapeutic goal will be to achieve improved outcomes by applying this important knowledge with the possibility of immunotherapy. Current pharmacological treatments after infarct and subsequent heart failure include angiotensin-converting enzyme inhibitors, angiotensin blockers, and aldosterone antagonists. Although these agents can have direct effects on cardiomyocytes, studies such as these raise the questions of whether some treatments may be altering the immune system and whether these changes could be contributing to the therapeutic effect. Angiotensin II and aldosterone have been shown to alter macrophage activation and polarization and cardiac remodeling. In addition, as we delineate the exact role of subpopulations of DCs, T cells, other myeloid and immune cells, this knowledge can be applied to devise new treatments or combination therapies that target the immune cells to promote beneficial remodeling.

Disclosures

None.

References


**KEY WORDS:** Editorials | fibrosis | immunology | inflammation | myocardial infarction | ventricular remodeling
Immune Cell Modulation of Cardiac Remodeling
Richard M. Mortensen

_Circulation_. 2012;125:1597-1600; originally published online March 2, 2012;
doi: 10.1161/CIRCULATIONAHA.112.097832

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/125/13/1597

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/