Regulating Repair
Regulatory T Cells in Myocardial Infarction

Matthias Nahrendorf, Filip K. Swirski

Ischemic injury to the myocardium is likely the most frequent but certainly the most deadly contemporary wound in humans. The lack of oxygen jeopardizes cardiac resident cells, which include myocytes, fibroblasts, endothelial cells, and cardiac macrophages. These cells then die or react by releasing danger signals, which systemically alert the immune system. The most numerous responders are myeloid cells, including neutrophils, monocytes, and macrophages. The past decade elucidated the time line of response, in which consistent high-rate inflammatory neutrophil and monocyte recruitment dominate the first hours to days. After day 4, inflammation begins to resolve, and recruited monocytes give rise to less inflammatory reparative macrophages. These 2 phases, a first inflammatory and a second resolution phase, are essential for infarct healing. In mice with atherosclerosis, phases, a first inflammatory and a second resolution phase, are rise to less inflammatory reparative macrophages. These 2

...inflammation, resulting in the persistence of inflammatory macrophages accumulating per mg infarct tissue, represents a small Treg:macrophage ratio. This clearly eliminates Tregs as foot soldiers of the response. However, even a small number of leukocytes can be important. The question then is, does this accumulation matter?

Weirather et al induced MI in Foxp3DTR mice, which allowed the investigators to deplete Tregs. In these mice, infarct size was increased, resolution of infarct inflammation was impaired, and neutrophil and Ly6Chigh monocyte numbers were augmented. Moreover, the gene expression profile from macrophages isolated from 5-day-old infarcts was biased toward inflammation, and factors typically associated with healing, such as transforming growth factor-β, osteopontin, and transglutaminase factor XIII, were decreased. The latter was previously identified as a prominent marker of inflammatory classical mouse monocytes by the ImmGen consortium (www.immgen.org), highlighting that the simple M1/M2 categorization of macrophages is far from precise, and suggesting that local factors may change specific genes in a manner that overrides the M1/M2 classification. Taken together, absence of Tregs led to impaired transition toward resolution of inflammation, resulting in the persistence of inflammatory macrophages and delayed healing (Figure).

When Tregs were depleted with a CD25 antibody 8 days before MI, post-MI survival was impaired, which did not occur in Foxp3DTR mice. However, antibody depletion led to more numerous neutrophil and Ly6Cint monocyte in infarcts. Treatment with a superagonistic anti-CD28 antibody expanded Tregs 2-fold in blood and heart-draining lymph nodes,...
shifted the macrophage gene expression toward inflammation resolution, improved infarct matrix repair, and reduced infarct mortality. Coculture experiments suggested that Tregs may modulate macrophage phenotype in vitro via secretion of IL-10 and IL-13.

Collectively, the Frantz group describe an interesting observation in 2 different models of Treg depletion and 1 model of Treg activation: an altered abundance of these cells correlated with an altered macrophage phenotype and outcome post-MI. The study adds to the increasing evidence that heart macrophages are important in the evolution of heart failure, and reports a novel, potentially clinically important mechanism of how cardiac macrophage phenotype is steered. The data raise several interesting questions. For example, where and how do Tregs interact with myeloid cells? On the one hand, recent studies indicate that IL-10 is a critical homeostatic factor for macrophages.16 On the other hand, the low absolute numbers of Tregs vis-a-vis myeloid cells in the infarct raises the question of whether additional interactions are important elsewhere. Can Tregs influence the supply of cells in other locations? Previously, Tregs were shown to influence the action of hematopoietic progenitors in the bone marrow.17 Can Tregs interact with monocyte progenitors and change their phenotype before they enter inflamed tissues? Recent studies have shown that cell intrinsic factors, such as the orphan nuclear hormone receptor, nuclear receptor subfamily 4, group a, member 1 (Nr4a1) expressed in monocytes regulate the emergence of Ly6Clow monocytes in blood and regulate the infarct macrophage phenotype.4,18 Another regulator of macrophage phenotype after MI is the master transcription factor IRF5 (interferon regulatory factor 5).19 In light of the Treg data discussed above, it would be interesting to explore whether these mechanisms are coupled or independent. Overall, it is likely that the infarct macrophage phenotype results from an integration of multiple inputs, including cell-intrinsic, systemic, and local factors. Going forward, we will need to identify viable avenues for a therapeutic intervention that modulates infarct inflammation and prevents post-MI heart failure. Additional work will show whether Treg activation is such an option for patients with MI.

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None.

**References**


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