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EDITORIAL COMMENT

The Role of Macrophages in Nonischemic Heart Failure*

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The mammalian heart contains a population of resident macrophages that expands in response to injury through the recruitment of circulating monocytes (1). After myocardial infarction, the sudden death of a large number of cardiomyocytes releases danger signals, mobilizing monocytes in the bone marrow and possibly also in extramedullary sites, such as the spleen. Induction of CC chemokines, such as CC motif chemokine ligand 2, in the infarcted myocardium recruits abundant monocytes that express the chemokine receptor CCR2, and exhibit a proinflammatory phenotype (2,3). $CCR2^+$ monocytes and macrophages play an important role in the clearance of necrotic cardiomyocytes and in cardiac repair after infarction, but also contribute to the pathogenesis of adverse cardiac remodeling (2). Although macrophages have been extensively implicated in the reparative and remodeling responses to myocardial infarction, their role in chronic nonischemic heart failure remains unclear. In mouse models of heart failure associated with left ventricular pressure overload, and in heart failure with preserved ejection fraction patients, the density of myocardial macrophages is significantly increased (4,5). However, the mechanisms of recruitment and activation of cardiac macrophages in response to chronic pressure overload and their functional role in the development of heart failure are poorly understood.

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In this issue of *JACC: Basic to Translational Science*, Patel et al. (6) demonstrate an important role for $CCR2^+$ macrophages in the pathogenesis of fibrosis, hypertrophy, and cardiac dysfunction in the pressure-overloaded heart. In a mouse model of transverse aortic constriction, a significant increase in circulating $Ly6C^{hi}CCR2^+$ monocytes was associated with a marked expansion of myocardial $CCR2^+$ macrophages, driven by cardiac induction of CC chemokines. Blocking CCR2 through early administration of the small molecule CCR2 antagonist RS-504393, or through treatment with the anti-CCR2 monoclonal antibody MC21, inhibited myocardial infiltration with $CCR2^+$ macrophages, abrogated the expansion of T cells in heart-draining mediastinal lymph nodes, and reduced left ventricular hypertrophy after 1 week of pressure overload. Moreover, 4 weeks after transverse aortic constriction, MC21-treated mice exhibited significantly attenuated systolic dysfunction and profoundly reduced cardiac interstitial fibrosis, in comparison to immunoglobulin G-treated animals.

The study adds to a growing body of evidence suggesting that chemokine-driven, macrophage-mediated inflammation plays a critical role in the pathogenesis of pressure overload-induced heart failure. The findings not only support the significance of $CCR2^+$ macrophages as cellular effectors of myocardial fibrosis, hypertrophy, and dysfunction in nonischemic heart failure, but also open new research directions by raising several important questions.

WHAT IS THE STIMULUS FOR THE EXPANSION OF MACROPHAGES IN PRESSURE-OVERLOADED HEARTS?

In conditions associated with extensive cellular necrosis, the release of danger signals mobilizes bone

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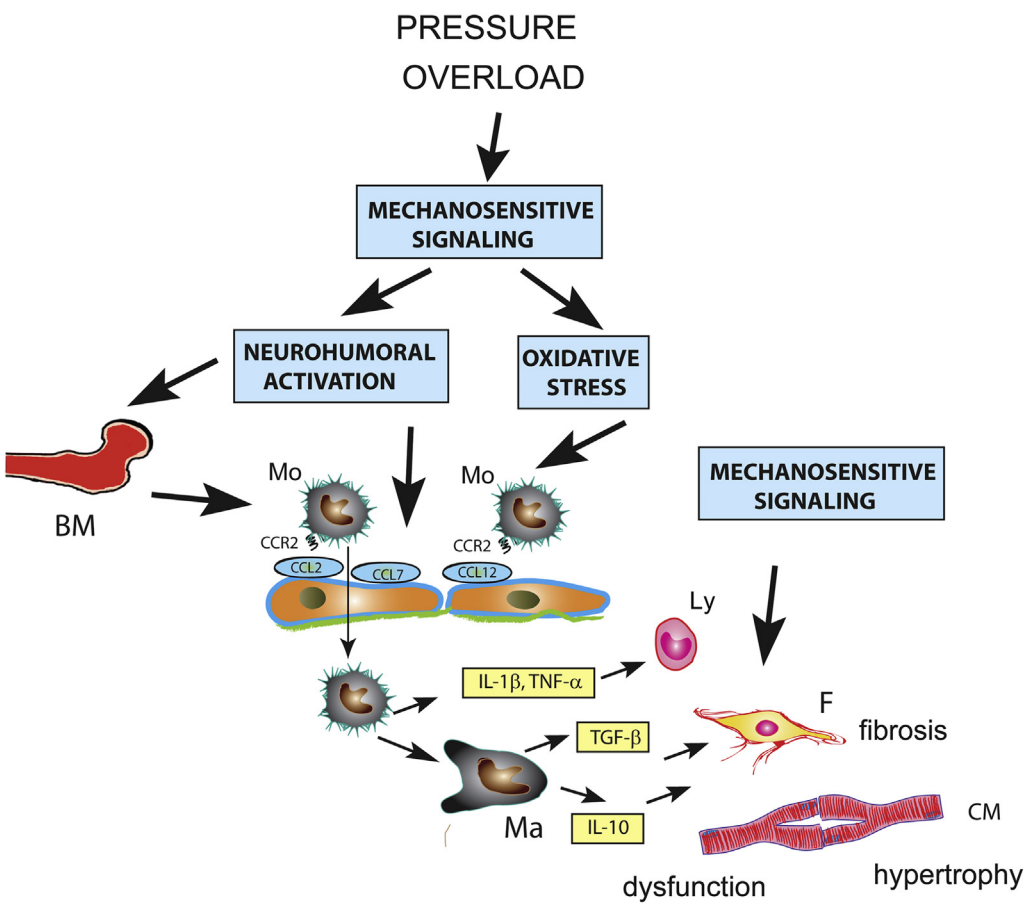
FIGURE 1 Expansion and Activation of Macrophages in the Pressure-Overloaded Myocardium



Pressure overload activates neurohumoral pathways and increases oxidative stress, mobilizing bone marrow (BM)-derived monocytes (Mo). Angiotensin II- and reactive oxygen species-triggered induction of chemokines in the pressure-overloaded myocardium mediates recruitment of monocytes expressing CCR2. $CCR2^{+}$ monocytes secrete proinflammatory cytokines (such as IL-1β and tumor necrosis factor-α) and may activate lymphocytes (Ly), causing dysfunction of the remodeling heart. Monocytes may differentiate into macrophages (Ma) that secrete transforming growth factor-βs and IL-10, activating fibroblasts (F) and promoting cardiomyocyte (CM) hypertrophy.

marrow monocytes and triggers intense chemokine-driven inflammation (7). However, in the pressure-overloaded myocardium, cardiomyocyte necrosis is limited, and the molecular link between mechanical stress and monocyte mobilization is unclear. Several mechanisms may explain the observed induction of chemokines and subsequent infiltration of the pressure-overloaded myocardium with proinflammatory macrophages (**Figure 1**). First, activation of neurohumoral cascades may mobilize bone marrow and splenic monocytes and may upregulate inflammatory signaling in the myocardium. Angiotensin II is known to activate proinflammatory signaling in both vascular cells and monocytes, acting at least in part through chemokine induction (8). Second, increased oxidative stress in the pressure overloaded myocardium, triggered through neurohumoral activation or via activation of mechanosensitive signaling pathways, may promote chemokine-mediated recruitment of inflammatory cells (9). Third, mechanosensitive signaling may exert direct proinflammatory effects on resident myocardial cells (including cardiomyocytes, fibroblasts, and vascular cells), triggering local induction of cytokines and chemokines that mediate recruitment of monocytes (10). Thus, cellular necrosis is not necessary for the activation of an inflammatory program in the remodeling myocardium.

DO THE ACTIONS OF THE CC CHEMOKINE/CCR2 AXIS INVOLVE EXCLUSIVELY EFFECTS ON MACROPHAGES?

The authors suggest that the protective effects of CCR2 blockade may involve actions on monocytes and macrophages. Although this is plausible, it should be emphasized that CCR2 expression has also been reported in many other cell types, including lymphocyte subsets, fibroblasts, and vascular cells. Several in vitro studies have suggested direct effects of CCR2 ligands on fibroblast phenotype and gene expression (11); however, evidence supporting the notion that chemokine-driven myocardial fibrosis is mediated through direct actions on cardiac fibroblasts is lacking (12). The crucial role of lymphocyte subpopulations in cardiac fibrosis (13), and the involvement of the CC motif chemokine ligand 2/CCR2 axis in regulation of lymphocyte responses (14) suggest that the effects of CCR2 blockade may be mediated at least in part, through the modulation of lymphocyte recruitment and activation.

WHAT IS THE MOLECULAR BASIS FOR THE EFFECTS OF CCR2$^+$ MACROPHAGES IN THE PRESSURE-OVERLOADED HEART?

Macrophages exhibit remarkable functional heterogeneity and are capable of expressing a wide range of genes. After tissue injury, dynamic microenvironmental changes induce dramatic alterations in the phenotypic characteristics of macrophages. In the infarcted myocardium, early release of danger signals induces a proinflammatory and phagocytotic macrophage phenotype. The ingestion of apoptotic cells has been proposed to trigger a regulatory phenotype in macrophages, inducing expression of anti-inflammatory mediators (such as interleukin [IL]-10 and transforming growth factor-β). Fibrogenic and angiogenic macrophage subsets have also been identified and may play an important role in repair of the infarcted heart. Moreover, macrophages may also contribute to extracellular matrix remodeling by producing matrix metalloproteinases and their inhibitors.

The molecular signals that may mediate the profibrotic and hypertrophic actions of macrophages in the pressure-overloaded myocardium remain unknown. The current study suggests that macrophage-driven T-cell expansion may play an important role in adverse remodeling; the specific proinflammatory cytokines that may mediate lymphocyte activation are unclear. The direct effects of macrophage-derived mediators on fibroblast activation may also be involved. A recent study suggested that IL-10 secreted by myeloid cells may be an important fibrogenic signal in experimental models of cardiac fibrosis (5). Macrophage-derived secretion of transforming growth factor-β family members may also contribute to activation of a fibrogenic program. Macrophages may also promote fibrosis by releasing tissue inhibitors of metalloproteinases, thus exerting potent matrix-preserving actions (15). Considering the wide range of mediators secreted by macrophages, it is unlikely that the profibrotic actions of CCR2$^+$ cells are mediated through the release of a single molecular signal.

IS CHEMOKINE-DRIVEN INFLAMMATION A THERAPEUTIC TARGET IN HUMAN HEART FAILURE?

The protective effects of CCR2 blockade reported in the current study may have direct therapeutic implications for patients with heart failure. On the basis of these experimental observations, it could be proposed that CCR2 inhibition may attenuate myocardial dysfunction and inhibit fibrosis in patients with heart failure with a prominent pressure overload pathophysiology. It should be emphasized that, although this approach may seem to be promising, therapeutic translation in human heart failure poses major challenges. Human heart failure is pathophysiologically heterogeneous and cannot be recapitulated by a single animal model. Successful translation may require the identification of patient subpopulations with a prominent inflammatory response that may benefit from inhibition of the chemokine axis. Moreover, the need for chronic treatment generates major concerns regarding the risk profile of the approach. Chronic administration of an anti-inflammatory agent may carry significant risks by inhibiting reparative and protective effects of inflammation. CCR2 signaling has been implicated in the activation of the angiogenic process (16); thus, inhibition of the CC chemokine/CCR2 axis may also perturb angiogenic responses, necessary to preserve perfusion in subjects with coexisting ischemic heart disease. Studies aimed at understanding the involvement of cardiac macrophages in human patients are critical to explore the potential value of chemokine targeting in heart failure.

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