Mediators Secreted by Myeloid Cells May Protect and Repair the Infarcted Myocardium

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Myeloid-derived growth factor (C19orf10) mediates cardiac repair following myocardial infarction

Korf-Klingebiel et al

In the infarcted myocardium, cardiomyocyte necrosis activates inflammatory cascades resulting in recruitment of myeloid cells that have been suggested to extend ischemic injury, but also clear the infarct from dead cells and matrix debris, and stimulate the reparative process. A growing body of evidence suggests that subsets of myeloid cells may exert protective actions on the infarcted myocardium. A recently published study in *Nature Medicine*, identified myeloid-derived growth factor as an antiapoptotic and angiogenic mediator that is secreted by a subset of macrophages and may protect the infarcted heart from adverse remodeling.

The adult mammalian heart has negligible regenerative capacity. Cardiomyocyte necrosis triggers an intense inflammatory reaction leading to the formation of a collagen-based scar. The infarcted myocardium is rapidly infiltrated with abundant myeloid cells, which are primarily localized in the border zone and interact with viable cardiomyocytes. Over the past 3 decades, researchers have struggled to identify detrimental and protective inflammatory signals, to design therapeutic strategies for patients with myocardial infarction. A large body of experimental evidence suggested that neutrophils and proinflammatory monocytes may extend ischemic injury, inducing cytotoxic effects on surviving cardiomyocytes and promoting extracellular matrix degradation. In experimental models, targeted inhibition of β2 integrins failed to reduce infarct size. Unfortunately, in human patients, 3 small clinical trials targeting β2 integrins failed to reduce infarct size.

More recently, several studies have focused on the protective actions of leukocyte subpopulations. In experimental models, cell therapy with bone marrow mononuclear cells enhanced function of the infarcted heart. These observations suggested that myeloid cell subsets secrete a broad repertoire of paracrine factors that may attenuate pathological remodeling, induce neovascularization, and even promote myocardial regeneration. Because mononuclear cells are highly heterogeneous, further experimentation focused on identification of specific bone marrow–derived populations with protective actions. In both animal models and human patients, bone marrow cell populations expressing the chemokine receptor CXCR4 (the ligand for the CXC chemokine stromal–derived–factor-1, also known as CXCL12) attracted significant interest. In mice, mobilization of CXCR4+ bone marrow–derived cells reduced infarct size and improved cardiac function after myocardial infarction. In the Bone Marrow Transfer to Enhance ST-segment–elevation Infarct Regeneration 2 (BOOST-2) clinical trial, intracoronary therapy with bone marrow cells enhanced functional recovery in patients with ST-segment–elevation myocardial infarction. Only a small fraction of cells were retained in the infarct; these cells expressed CXCR4. However, the basis for the protective actions of the CXCR4+ subpopulation of bone marrow–derived cells remains unclear.

In a recently published study in *Nature Medicine*, Korf-Klingebiel et al used secretome analysis of CXCR4+ bone marrow cells from patients enrolled in the BOOST-2 trial to identify novel bone marrow–derived mediators with protective actions on the infarcted heart. Thorough transcriptomic analysis identified 42 sequences with structural features consistent with active secretion. After cloning the cDNAs of each of these proteins into expression plasmids and transfection into HEK-293 cells, the authors screened the conditioned supernatants for cytoprotective effects on neonatal rat ventricular cardiomyocytes, and identified 1 protein that inhibited caspase-3 and caspase-7 activity and enhanced metabolic activity. They christened this protein myeloid-derived growth factor (MYDGF). MYDGF was highly upregulated in both human and mouse infarcts and was predominantly expressed by CXCR4+ monocytes and macrophages. To examine the role of MYDGF in myocardial infarction, the authors generated MYDGF null mice. In a model of myocardial ischemia/reperfusion, MYDGF null mice had increased infarct size, worse cardiac dilation, and more pronounced systolic dysfunction, compared with wild-type animals. Experiments using chimeric mice demonstrated that MYDGF derived from inflammatory cells was responsible for the protective actions. Two gain-of-function approaches further supported the protective
actions of MYDGF on the infarcted myocardium. Systemic administration of recombinant MYDGF immediately after reperfusion, and adenovirus-mediated gene therapy with full length MYDGF reduced infarct size and attenuated systolic dysfunction after myocardial infarction.

The authors identified 2 major mechanisms implicated in MYDGF-induced cardioprotection (Figure). First, MYDGF transduces pro-survival signals in cardiomyocytes by activating a phosphatidylinositol 3-kinase/Akt pathway. Second, although dispensable in developmental angiogenesis, MYDGF is required to support neovessel formation in the infarct. The angiogenic effects of MYDGF are associated with proliferative actions on endothelial cells, mediated through activation of a mitogen-activated protein kinase/signal transducer and activator of transcription 3 pathway.

The study uses an impressive range of experimental approaches to identify and characterize a novel myeloid cell–derived mediator with protective actions on the infarcted heart. The findings highlight the protective potential of selected leukocyte subpopulations, and suggest a novel and promising treatment strategy for myocardial infarction, opening new directions in the biology of myeloid cells and in translational cardiovascular research.

**Myeloid Cells Subsets With Cardioprotective and Reparative Properties**

Myeloid cells exhibit remarkable heterogeneity and phenotypic plasticity. In vivo, macrophages may not function as polarized M1 and M2 cells, but rather acquire more nuanced phenotypes in response to microenvironmental cues. Angiogenic, fibrogenic and regulatory macrophage subsets have been identified in injured and remodeling tissues and may orchestrate reparative responses. The heart contains relatively small numbers of resident macrophages, after injury, the cardiac macrophage population is expanded through recruitment of monocyte-derived cells. Emerging evidence suggests that macrophage subsets may acquire phenotypes that regulate the response of cardiomyocytes to injurious stimuli. Recently published findings in mouse models of neonatal cardiac injury suggest that distinct neonatal macrophage lineages may promote cardiac regeneration, stimulating cardiomyocyte proliferation. The report by Korf-Klingebiel et al demonstrates for the first time that the adult infarcted heart recruits a subset of CXCR4high macrophages that protects cardiomyocytes from apoptosis, while exerting potent angiogenic properties.

**The Mechanism of Recruitment of Protective Myeloid Cells**

The healing infarct sequentially recruits several subpopulations of monocytes with different functional properties through activation of distinct chemokine/chemokine receptor interactions. During the early proinflammatory phase, induction of the chemokine CCL2/monocyte chemoattractant protein-1 attracts proinflammatory monocytes that play an important role in phagocytotic clearance of dead cells and matrix debris. Recruitment of anti-inflammatory and reparative monocyte subsets through interactions involving the

![Figure](http://circres.ahajournals.org/) Cardioprotective signaling pathways activated by myeloid-derived growth factor (MYDGF) in the infarcted myocardium. Myeloid cells infiltrating the infarct secrete MYDGF. MYDGF stimulates phosphatidylinositol 3-kinase (PI3K)/Akt, a prosurvival pathway, in cardiac myocytes, resulting in inhibition of proapoptotic molecules. In endothelial cells, MYDGF induces proliferation and neovessel formation through activation of mitogen-activated protein kinase (MAPK)1/3 and signal transducer and activator of transcription 3 (STAT3). Activation of these pathways reduces infarct size and attenuates remodeling after myocardial infarction.
chemokine receptors CCR5 and CX3CR1 may orchestrate a dynamic change in the infarct environment, leading to suppression of proinflammatory signaling and activation of the reparative process. What is the mechanism of recruitment for the MYDGF-expressing cardioprotective myeloid cells? The high expression of CXCR4 by these cells suggests that stromal cell–derived factor-1 may play a prominent role in their recruitment. Extensive evidence suggests that stromal cell–derived factor-1 treatment exerts cardioprotective effects on the infarcted heart; the effects of stromal cell–derived factor-1 may be mediated, at least in part, through recruitment of MYDGF/CXCR4high myeloid cells.

The Cellular Effects of MYDGF
In vitro studies and associative in vivo observations suggest that the mechanisms of MYDGF-mediated cardioprotection may involve antiapoptotic actions on ischemic cardiomyocytes and angiogenic effects. These intriguing observations raise several important questions on the mechanistic basis for MYDGF-mediated actions. Which receptor transduces MYDGF signals? In addition to any direct effects, MYDGF may modulate actions of other cytokines and growth factors. What are the major cellular targets of MYDGF? Although in vitro experiments suggest that MYDGF affects endothelial cell behavior and enhances cardiomyocyte survival, subpopulations of immune cells, fibroblasts or vascular smooth muscle cells may also respond to the cytokine. The relative significance of specific cellular effects in mediating the protective actions of MYDGF on the infarcted heart is unknown. Moreover, the cellular specificity of the effects of MYDGF on phosphatidylinositol 3-kinase/Akt, signal transducer and activator of transcription 3, and mitogen-activated protein kinase signaling remains to be investigated.

MYDGF Therapy in Infarction
The impressive effects of MYDGF therapy on survival of ischemic cardiomyocytes and on the size of the infarct support the therapeutic potential of this approach for patients with myocardial infarction. However, a word of caution should be raised about the challenges of clinical translation, even when the approach is supported by strong animal model data. Several strategies targeting the inflammatory cascade have produced impressive results in experimental models, but failed in clinical studies. The experience with β2 integrin inhibition illustrates the translational challenges. The limitations of clinically relevant end points in mice undergoing infarction protocols, and the complexity of the clinical context greatly diminish the value of animal investigations in predicting translational success. Despite these cautionary statements, this investigation generates a high level of enthusiasm not only because it provides novel insights into the functions of MYDGF but also because it serves as a prototypical example of a systematic approach to identify protective paracrine effects of cell therapy.

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Disclosures
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