Inflammation as a Driver of Adverse Left Ventricular Remodeling After Acute Myocardial Infarction

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ABSTRACT

Treatment of acute myocardial infarction (AMI) has improved significantly in recent years, but many patients have adverse left ventricular (LV) remodeling, a maladaptive change associated with progressive heart failure. Although this change is usually associated with large infarcts, some patients with relatively small infarcts have adverse remodeling, whereas other patients with larger infarcts (who survive the first several days after AMI) do not. This paper reviews the relevant data supporting the hypothesis that individual differences in the intensity of the post-AMI inflammatory response, involving 1 or more inflammatory-modulating pathways, may contribute to adverse LV remodeling. It concludes by outlining how individual variations in the inflammatory response could provide important novel therapeutic targets and strategies. (J Am Coll Cardiol 2016;67:2050–60) © 2016 by the American College of Cardiology Foundation.

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reatment of patients presenting with an acute myocardial infarction (AMI) has evolved enormously over the past several years. Percutaneous coronary intervention (PCI), when performed in the first hours after symptom onset, decreases acute mortality rates and reduces the incidence of compromised left ventricular (LV) function when measured within the first week after AMI (1). Although most patients treated by PCI within the recommended time frame also do well over the long term, in a subgroup of patients, progressive adverse LV remodeling and, ultimately, heart failure develop, despite implementation of secondary prevention measures, including beta-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, and aspirin. The traditional explanation for this phenomenon attributes it to high LV wall stress developing after a large AMI. Thus, the left ventricle dilates as a compensatory mechanism to improve LV pump function (through the Frank-Starling mechanism). LV dilation, by the Laplace relationship, increases wall stress, thus begetting further LV dilation. These changes, through a positive feedback loop, can lead to progressive adverse LV remodeling and to heart failure.

The purpose of this hypothesis-generating paper is 2-fold. The first is to review the relevant data indicating that the cause of adverse remodeling cannot be entirely ascribed to this traditional mechanistic view. This perspective is reinforced by newly analyzed (but previously published) data indicating that, in patients who survive the first several days of an AMI, a large infarct is neither necessary nor sufficient for progressive adverse LV remodeling to occur. This finding has important implications for the second purpose of this paper, which is to explore the hypothesis that...
persistent increased activation of inflammatory pathways importantly contributes to progressive adverse LV remodeling.

**IMPERFECT LINK BETWEEN INFARCT SIZE AND ADVERSE LV REMODELING**

That infarct size is an important determinant of adverse remodeling has been demonstrated by several studies in which larger infarct size correlated with greater adverse LV remodeling. Thus, using LV ejection fraction (LVEF) determined by left ventriculography as an index of infarct severity, Schächinger et al. (2) demonstrated an inverse relationship between baseline LVEF (obtained 4 days post-AMI) and the increase in LV end-systolic volume (LVESV) and LV end-diastolic (LVEDV) volume measured 4 months later (Figure 1). Other investigators reported similar findings (3–5).

In addition to demonstrating that patients with reduced LVEF have a greater likelihood of developing progressive enlargement in LVESV and LVEDV over time, Figure 1 also shows that a group of patients with normal or nearly normal LVEF several days after AMI can have progressively increased LVESV and LVEDV. Although the percentage of such patients with progressive dilation is considerably lower than that of the patients who start out with an abnormal LVEF, the number is notable. This finding suggests that mechanisms leading to adverse LV remodeling other than initial infarct size are at play.

LVEF, however, is not a precise measure of infarct size. In the context of decreased myocardial function, compensatory mechanisms attempt to maintain cardiac output. Impaired pump function leads, through the Frank-Starling mechanism, to increased LVEDV and thereby to increased myocardial fiber stretch. The increased stretch augments the force of contraction so that LVEF and cardiac output are maintained, despite the decreased LV pump function caused by a large infarct. Thus, LVEF may be maintained at nearly normal levels, despite a large infarct, consequent to the compensatory increase in LVEDV.

The relationship, or lack thereof, between infarct size and adverse LV remodeling can be approached more directly by data derived from cardiac magnetic resonance (CMR) imaging, which permits an estimate of infarct size through measurement of late gadolinium enhancement. Figure 2 shows a new presentation of data from a study performed by 2 of the present authors (E.W. and R.B.) in which the relationship between baseline infarct size and subsequent adverse LV remodeling was compared (5). The data displayed in Figure 2 were entered into spreadsheets and were extracted and reanalyzed so that the relationship between initial infarct size and absolute change in LVEDV could be specifically analyzed. CMR was performed within a week after ST-segment elevation myocardial infarction, with follow-up CMR 4 months later. Acute infarct size was a significant predictor of adverse cardiac remodeling: the greater the infarct size, the greater the subsequent increase in both LVEDV (p < 0.001) (Figure 2) and LVESV (p = 0.001). Moreover, in a multivariate analysis, infarct size more strongly predicted remodeling than did initial LVEF or LVESV.

This finding makes pathophysiological sense in terms of the Frank-Starling compensatory mechanism. In other words, the infarct-related decreased LV pump function puts into motion the conditions for progressive adverse LV remodeling. It follows that PCI, by rapidly restoring flow in the infarct-related artery, limits infarct size and thereby minimizes the risk of progressive LV remodeling and heart failure.

Careful examination of the data shown in Figure 2, which displays the relationship between adverse remodeling and actual infarct size, reveals that of the group of patients with 1) smaller infarct sizes (<18.5% of LV mass), in a subgroup of ~15%, progressive adverse LV remodeling (defined as an increase in LVEDV index of >10 ml/m²) nonetheless developed; and 2) larger infarct sizes (≥18.5% of LV mass), approximately 40% had progressive adverse LV remodeling (p = 0.008), but therefore approximately 60% did not. Baseline differences (e.g., the presence of hypertension or hypercholesterolemia, tobacco smoking, diabetes, family history of coronary artery disease, among others) did not explain the differences in the amount of adverse remodeling between the patients with small infarcts and those with large infarcts.

This analysis raises the following questions: 1) if a large infarct is not a necessary cause of adverse remodeling, what then is the cause of the adverse remodeling in such patients? and 2) if a large infarct is not a sufficient cause of adverse remodeling, what accounts for the different propensity for adverse LV remodeling to develop in such patients?

The answers to these questions are undoubtedly complex and most likely involve multiple mechanisms. In this paper, we chose to focus on the experimental and clinical data suggesting that an excessive inflammatory response is, in addition to infarct size, a possible major contributor to the

**ABBREVIATIONS AND ACRONYMS**

- AMI = acute myocardial infarction
- CMR = cardiac magnetic resonance
- CRP = C-reactive protein
- IFN = interferon
- IL = interleukin
- LV = left ventricular
- LVESV = left ventricular end-systolic volume
- LVEF = left ventricular ejection fraction
- LVEDV = left ventricular end-diastolic volume
- MMP = matrix metalloproteinase
- MSC = mesenchymal stem cell
- PCI = percutaneous coronary intervention
- ROS = reactive oxygen species
- TGF = transforming growth factor
- TIMP = tissue inhibitor of metalloproteinases
- TNF = tumor necrosis factor
adverse remodeling that occurs in the days, weeks, and months after AMI.

**ROLE OF INFLAMMATION IN ADVERSE LV REMODELING**

Inflammation is a critical component of tissue healing. However, an intriguing concept has emerged, suggesting that these same inflammation-related processes leading to tissue healing are not adequately modulated in certain subgroups of patients and thereby contribute to adverse LV remodeling after AMI. There are no data definitively proving the validity of this concept, but several studies are compatible with it. In preclinical studies, for example, myocardial expression levels of the proinflammatory cytokines interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β, measured 8 and 20 weeks after AMI in a rat model, were shown to be significantly associated with LV end-diastolic diameter measured at study termination (6); in IL-1 receptor 1 (IL-1R1) knockout mice, lack of IL-1R1 protected against the development of ventricular dilation (7); administration of the IL-1 receptor antagonist, anakinra, shortly after AMI in both mouse and rat AMI models reduced LVEDV measured 7 days after AMI (8).

To our knowledge, virtually all clinical studies relating inflammatory biomarker levels to subsequent adverse LV remodeling after AMI used biomarker levels measured in the first hours or days after AMI onset. This approach is problematic for deriving insights regarding the concept we are examining in this paper because acute increases in biomarkers may reflect the severity of the infarct, rather than indicating a chronic persistent inflammatory state contributing to adverse LV remodeling. The only study measuring biomarkers late after AMI that we could find was that performed by Ørn et al. (9). These investigators found, patients with ST-segment elevation myocardial infarction who were treated with PCI, that IL-1β levels measured pre-, 2, and 7 days post-PCI predicted LVESV index and LVEDV index measured by CMR at 1 year. However, and most importantly for the concept we are considering, these measures of adverse LV remodeling were also predicted by *IL-1β levels measured 2 months post-PCI*.

Although clinical evidence relating progressive adverse LV remodeling to an excessive and persistent inflammatory state after AMI is sparse, additional evidence derives from biomarker studies obtained in patients with chronic heart failure. Notably, all-cause mortality in hospitalized patients with dilated cardiomyopathy was higher in patients with high-sensitivity (hs) C-reactive protein (hs-CRP) levels >3.90 mg/l versus patients with levels <3.90 mg/l (10); moreover, CRP levels independently predicted these events. Additionally, in a multicenter clinical trial of Left ventricular (LV) angiography was obtained 4.3 days after percutaneous coronary intervention and was repeated 4 months later. Left ventricular remodeling developed over time in both patients with a reduced baseline ejection fraction (EF) (orange area) and in patients with a normal baseline ejection fraction (blue area). Adapted with permission from Schächinger et al. (2). LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; vol = volume.
1,200 patients with advanced heart failure (11), increasing circulating levels of TNF, IL-6, and the soluble TNF receptors sTNFR1 and sTNFR2 were associated with increased mortality.

Thus, although neither basic evidence nor clinical evidence exists proving that dysregulated inflammation post-AMI is a causative factor of adverse LV remodeling, an increasing body of data is compatible with this mechanism playing such a role.

The following section presents an overview of the inflammation-related processes triggered by AMI to illustrate how complex these events are, and therefore how multiple opportunities exist by which slight alterations of 1 or more of the pathways involved in the healing response could predispose to adverse remodeling.

**INFLAMMATION-RELATED PROCESSES TRIGGERED BY AMI**

**INFLAMMATORY PHASE.** The Central Illustration depicts a model of the different phases of the healing response to AMI (12-16). It has been adapted from several excellent reviews on the topic (12,15,17), and the data derive, in the main, from studies performed in vitro and in animal models.

The injury incurred by cardiac myocytes and the extracellular matrix consequent to acute ischemic damage rapidly activates the complement cascade, which plays a critical role in the inflammatory response to AMI (18), by stimulating multiple pathways signaling tissue injury. Among these are damage-associated molecular patterns (19) that, by binding to pattern recognition receptors on or within cells of the innate immune system, inform these cells that injury is present. One family of these pattern recognition transmembrane receptors—the Toll-like receptors (TLRs)—activates nuclear factor-κB (NF-κB), which initiates multiple inflammatory cascades, including the release of pro-IL-1β and pro-IL-18 (20). Danger-associated molecular pattern also activate the nucleotide-binding oligomerization domain-like receptor family of cytosolic proteins, certain of which induce the assembly of large caspase-1-activating complexes called inflammasomes (21). When the complex is assembled in response to damage- or pathogen-associated molecular patterns, caspase-1 is activated and converts pro-IL-1β and pro-IL-18 to their active forms, which stimulate many inflammatory pathways. Thus, the rapid activation of NF-κB and inflammasomes provides a 2-step process for supplying key components of the cytokine response to AMI. Acute ischemic injury also leads to the rapid generation of reactive oxygen species (ROS). These species have multiple signaling activities, including expression of chemokines, cytokines, and adhesion molecules, in part through activating inflammasomes.
All these processes contribute to recruitment of inflammatory cells to the injured myocardium. Neutrophils are the first inflammatory cells to migrate into the injured tissue. They phagocytize cellular debris, degrade extracellular matrix through the release of granules containing matrix metalloproteinases (MMPs), and generate ROS (13). These cells also secrete factors that are chemotactic to monocytes, thereby contributing additional stimuli to monocyte influx (12,23). Proinflammatory Ly6C\textsuperscript{high} macrophages arrive and phagocytize cellular detritus, thereby removing necrotic cardiomyocytes from the injured area. Other leukocytes such as T lymphocytes, B lymphocytes, dendritic cells, and natural killer cells begin to arrive on approximately the third day after ischemic insult. Through mechanisms that are the subject of continuing study, these cells aid in the transition of the proinflammatory phase of healing to the proreparative phase of healing. This shift may be accomplished through modulation of macrophage phenotype from Ly6C\textsuperscript{high} to Ly6C\textsuperscript{low}, production of anti-inflammatory cytokines (including, but not limited to, those indicated by the changing intensity of the green circles), and inhibition of matrix metalloproteinases (12,15,16). IFN = interferon; IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor.
monocytes constitute the initial monocyte population to home to the injured tissue (24). T lymphocytes also home to the injured tissue, as do natural killer (NK) cells, both of which are important players in the innate immune responses occurring in the infarcted myocardium (24). NK cells have a particularly complex role because they both interact with monocytes in the infarcted tissue, with resulting mutual stimulation of each cell type, and directly secrete interferon (IFN)-γ, TNF-α, and IL-1β. These actions help activate monocytes and macrophages and also help drive them to transdifferentiate into the M1 inflammatory macrophage phenotype (12,25,26). B lymphocytes have been shown to infiltrate into the infarcted myocardium, and although their precise role in the healing response is still largely unknown, depletion of B cells by use of specific antibodies has been shown to lead to a smaller infarct and improved LV function by day 14 post-AMI (24).

RESOLUTION OF THE INFLAMMATORY PHASE AND INITIATION OF THE REPARATIVE PHASE. Once the inflammatory response to acute tissue injury has accomplished those processes necessary for tissue repair to begin, mainly removal of necrotic debris and presumably prevention of infection of the necrotic tissue, processes that are still relatively poorly understood come into play that lead to suppression of inflammation and to tissue repair (15). These processes include reductions in proinflammatory Ly6C<sup>high</sup> mononuclear cells and M1 macrophages, as well as accompanying increases in the anti-inflammatory Ly6C<sup>low</sup> mononuclear cells and M2 macrophages (16). The reparative phase also includes what appears to be altered NK cell function; whereas in the early inflammatory phase of the response to AMI these cells exert proinflammatory effects, in the reparative phase, studies suggest that their mobilization and engraftment into the injured tissue may reduce adverse LV remodeling (27,28).

This changed cellular environment of the injured myocardium, occurring several days after the AMI, leads to the expression of cytokines involved in resolution of inflammation (Central Illustration). Monocyte-derived IL-10 is increased. This cytokine, secreted mainly by T-regulatory cells and M2 mononuclear cells (29), inhibits expression of the proinflammatory cytokines IL-1, IL-6, IL-8, and TNF-α and reduces myocardial necrosis and infarct size in mice (15,29,30). Levels of the cytokine transforming growth factor (TGF)-β increase, thereby inhibiting expression of proinflammatory chemokines, cytokines, and adhesion molecules (7,31). TGF-β also increases expression of cellular matrix proteins and exerts activities that inhibit degradation of matrix through suppression of protease activity, as well as enhanced production of tissue inhibitors of metalloproteinases (TIMPs) (15). Dendritic cells may orchestrate many of the changes responsible for transitioning from the proinflammatory response to the reparative phase of post-AMI healing (32).

INFLUENCES THAT MAY ALTER INFLAMMATORY RESPONSES, THEREBY PREDISPOSING TO ADVERSE REMODELING

As evident from the previous discussion, the inflammatory response to tissue injury is extraordinarily complex (12,15,17). As such, there are numerous steps at which genetic, epigenetic, or environmentally modulated changes in the expression or activities of molecules involved in regulating inflammatory responses could occur that may augment the intensity or prolong the duration of inflammatory responses—changes that, in turn, could predispose to adverse LV remodeling, thereby accounting for the disparity between infarct size and LV remodeling noted previously (Figures 1 and 2).

POSSIBLE GENETIC INFLUENCES. Genetic polymorphisms encoding inflammatory-related molecules, such as TNF-α and TNF-β, TGF-β1 and TGF-β2, and IL-1β, have been associated with an increased propensity to AMI (33,34). Conversely, the frequency of 2 different polymorphisms, each of which attenuates TLR4 receptor signaling, was significantly lower in patients with previous myocardial infarction compared with controls (35). These polymorphisms probably have functional consequences that affect inflammatory pathways (36) and could, by modulating the intensity or duration of inflammatory responses, alter the likelihood of plaque rupture. These same polymorphisms, we propose, may also predispose patients harboring them to an altered risk of adverse LV remodeling in the setting of AMI.

In addition, genome-wide association studies suggest a genetic link between inflammation and heart failure (and thus, indirectly, a link to adverse LV remodeling) (37).

POSSIBLE ROLE OF AUTOINFLAMMATORY DISEASE. Intriguingly, a large and compelling body of published reports has appeared over the past few years that describes genetic mutations and polymorphisms in genes encoding various components of the innate immune system leading to increased expression of many of the cytokines associated with activation of this system, such as IL-1β, IL-18, TNF-α, and IFN-γ (38). These genetic abnormalities, in turn, can lead to a diverse array of previously unexplained complex
clinical syndromes (39). Although these abnormalities are not yet linked to myocardial disease, investigators have suggested that the increased activity of the innate immune system caused by these genetic abnormalities could be causally related to atherosclerosis (40).

As an extension of this concept beyond the effects of inflammation on the arterial wall, we propose that some instances of adverse LV remodeling occur as a consequence of the existence of genetic alterations characteristic of autoimmune disease. We propose that patients with these genetic alterations may have no clinically apparent symptoms until a triggering event occurs that activates the expression of the altered genes, thus leading not only to inappropriately intense or prolonged inflammatory responses, but also to the status of the myocardium as the target tissue.

**POSSIBLE ROLE OF CHRONIC INFECTION.** Although controversial, many studies have suggested a role of chronic infection in the pathogenesis of atherosclerosis and of plaque rupture (41). Moreover, it was found that the number of pathogens ("pathogen burden") with which a patient was chronically infected (manifested by pathogen seropositivity) posed an incremental risk of AMI and death (42,43).

Any role these infectious agents play in the pathogenesis of atherosclerosis and AMI is probably related to their chronic and persistent activation of inflammatory pathways. Thus, these pathogens can increase ROS levels, activate NF-κB, and increase expression of chemokines and cellular adhesion molecules (41). Interestingly, T lymphocytes originating from the spleens of mice previously infected with cytomegalovirus (CMV) release IL-6, and conditioned medium from these cells induces monocyte chemoattractant protein (MCP)-1 expression in endothelial cells (44,45). This effect is partly the result of increases in circulating IFN-γ. It was also demonstrated that CMV-infected rats have higher serum levels of IL-2 and IL-4, and CMV-infected mice have elevated plasma IFN-γ and TNF-α levels (41).

Although the role of chronic infection in atherosclerosis and AMI has been largely ascribed to the effects of pathogen-induced augmented inflammatory activity on the vessel wall, thus leading to plaque formation and plaque instability, it is possible that the increased inflammatory activity these pathogens are capable of evoking could also have an impact on adverse LV remodeling.

**OTHER PROINFLAMMATORY INFLUENCES.** Many recognized risk factors predispose to atherosclerosis and AMI. Several of these, including smoking (46), obesity (47), hyperlipidemia (48), and diabetes (49), have also been found to exert proinflammatory effects. Other treatments that are believed to exert cardioprotective effects, including angiotensin-converting enzyme inhibitors (50), aspirin (51), and statins (52), have been associated with anti-inflammatory effects. These effects may not only relate to changes in the vessel wall, but they could also pertain to the known influence of several of these factors (e.g., diabetes and angiotensin-converting enzyme inhibitor therapy) on the extent of remodeling after AMI.

**IMPLICATIONS FOR POTENTIAL THERAPEUTIC TARGETS**

**TARGETING NEUTROPHIL ACTIVITY.** Neutrophils, as key effectors of innate immune responses, have activities that, if excessive, could lead to adverse LV remodeling. Examples include their capacities to degrade extracellular matrix through release of MMPs and to generate ROS (13,53). Loss of the CD11/CD18-integrin receptor (which allows neutrophils to bind to and traverse the endothelium) caused a significant decrease in infarct size (54,55).

Nonetheless, several clinical trials aimed at reducing the post-AMI neutrophil response have yielded disappointing results. The LIMIT AMI (Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial Infarction), HALT-MI (Hu23F2G Anti-Adhesion to Limit Cytotoxic Injury Following Acute Myocardial Infarction), and FESTIVAL (An Anti-CD11/CD18 Monoclonal Antibody in Patients with Acute Myocardial Infarction Having Percutaneous Transluminal Coronary Angioplasty) studies demonstrated that monoclonal antibodies targeting the CD18-integrin receptor failed to improve clinical outcomes (56-58).

It is important, however, to distinguish between the role of inflammation in determining infarct size and its role in determining adverse remodeling. The studies cited in the preceding paragraph mainly examined effects of treatment on infarct size or events at 30 days, but the studies neither measured nor addressed remodeling or long-term outcome.

Another explanation for the lack of benefit to patients from the CD11/CD18 blockade strategy is that it was too narrow an approach, given the complex array of cells and cytokines involved in the inflammatory and reparative phases of AMI (Central Illustration). In other words, the redundancy of pathways involved in these processes suggests that strategies aimed at modulating multiple facets of the post-AMI inflammatory response may be more efficacious than strategies focused on blocking a single agonist, or even a single cell type.
TARGETING INFLAMMATORY CYTOKINES. Inflammatory cytokines constitute intriguing therapeutic targets because of their pleiotropic effects on immune responses. Despite the promising results shown in animal models, however, clinical studies of therapies targeting inflammatory cytokines and chemokines have produced mixed results. Etanercept, a TNF-α inhibitor, failed to improve the clinical status of patients with heart failure significantly, thus resulting in termination of 2 large clinical trials (59). Interestingly, etanercept given to patients with sepsis, which is driven by systemic release of TNF-α, also failed to improve clinical outcomes (60) and was, in fact, associated with increased mortality rates at higher doses. Conversely, etanercept remains a cornerstone in treatment of chronic inflammatory diseases, such as rheumatoid arthritis (61). The underlying disease-specific mechanisms leading to beneficial versus deleterious effects of TNF-α inhibition remain unknown.

Attention has recently turned to therapeutic strategies that inhibit IL-1β (62). Pooled analysis of 2 small studies that examined the effect of anakinra on patients with AMI demonstrated a decreased incidence of new-onset heart failure in the treated group, although no significant effects on LV function or dimensions were observed (63,64). A third study, aimed at testing the effect of 2 anakinra doses on CRP levels and LV functional parameters in patients with ST-segment elevation myocardial infarction, is ongoing (NCT01950299) (65).

TARGETING THE INFLAMMASOME. Inflammasomes provide very promising targets for interventions designed to decrease the likelihood of adverse LV remodeling through exertion of anti-inflammatory effects. Thus, the inflammasomes, by activating multiple inflammatory molecules including IL-1β and IL-18, stimulate many inflammatory pathways. The NLRP3 inflammasome is thought to contribute to the pathophysiology of myocardial injury consequent to AMI (66). Although preclinical studies targeting different components of the NLRP3 inflammasome showed significant decreases in infarct size (67), interventions that directly inhibit inflammasome formation are not yet available for clinical trials.

MULTITARGETING STRATEGIES USING STEM CELLS. Stem cells have numerous effects on multiple pathways that could contribute, both separately and synergistically, to adverse remodeling and progressive deterioration of LV structure and function. They therefore constitute a potential post-AMI treatment option.

Inflammation. In the presence of inflammatory conditions in vitro, mesenchymal stem cells (MSCs) diminish proliferation and activation of T cells, dendritic cells, macrophages, and B lymphocytes and change the secretory profile of dendritic cells, T cells, and NK cells in ways that create an anti-inflammatory phenotype. This includes stimulating dendritic cells to decrease TNF-α and to increase IL-10 secretion, TH1 cells to decrease secretion of IFN-γ, TH2 cells to increase secretion of IL-4, and NK cells to decrease secretion of IFN-γ (68,69). In vivo, MSCs have been shown to exert anti-inflammatory activities (70,71).

Importantly, MSCs are not a single cell type; they have different properties depending on their tissue source and the conditions under which they are grown. Thus, the activities described for MSCs with certain characteristics do not necessarily reflect the activities of all MSCs. In addition, published reports relating to whether such MSC activities also reside in other stem cell types is much more limited (72). Finally, because most of the activities of MSCs result from their paracrine effects, it is possible that administration of the secreted products of MSCs alone could exert effects similar to those seen with administration of the cells.

Degradation of extracellular matrix. Importantly, papers by Lozito et al. (73,74) clarified MSC-related effects on MMPs and their inhibitors. Thus, MSCs can activate their proteolytic environment through their capacity to secrete MMPs. Presumably, this activity enables them to enhance their ability to migrate through tissue and to contribute to tissue remodeling. However, the overall activity of MSCs appears to be determined by the specific microenvironment in which they are located. For example, when exposed to proinflammatory cytokines and hypoxia, MSCs inhibited high levels of exogenous MMP-2 and MMP-9 through secretion of TIMP-2 and TIMP-1 (74). These activities, if present when administered exogenously to patients with AMI, could inhibit a key mechanism involved in adverse remodeling.

Angiogenesis. Patients with AMI may well benefit in the near and long term from the development of collateral vessels. Angiogenesis involves the coordinated expression of a very large number of factors (75,76), many of which are known to be secreted by stem cells, with multiple studies suggesting that stem cells can enhance angiogenesis (77,78). Thus, the potential of stem cells to improve collateral development adds an important mechanism by which stem cells could contribute to improved outcomes in AMI.

These multiple actions including (but not limited to) inhibition of inflammation and extracellular matrix degradation and enhancement of angiogenesis, provide a rationale for why stem cell administration could play a beneficial role in AMI outcome. However,
at this time, no definitive data indicate that stem cells prevent adverse LV remodeling post-AMI. Moreover, the results of clinical trials are conflicting, with some trials showing benefit and others showing no efficacy. These trials have been the subject of excellent meta-analyses and reviews (79,80). A reasonable conclusion at this time is that identification of the best stem cell, the most appropriate means of delivery (intra-, intramyocardial, intravenous at this time is that identification of the best stem cell, the most appropriate means of delivery (intra-, intramyocardial, intravenous), and the most appropriate time for delivery are still the subjects of ongoing investigation, so reliable conclusions about the ultimate efficacy of stem cell treatment for AMI cannot yet be drawn.

CONCLUSIONS

Our understanding of the factors that lead to adverse LV remodeling after AMI is still evolving. Although infarct size correlates with the development of adverse LV remodeling, some subsets of patients with small infarcts nonetheless have adverse LV remodeling, and some patients with large infarcts do not. Thus, there are undoubtedly many causes other than infarct size that contribute to adverse remodeling with progression to heart failure.

The processes involved in the initiation and resolution of inflammation are multiple and require tight regulation to achieve satisfactory tissue healing. It therefore seems plausible that slight deviations from normal could occur in 1 or more of the many pathways involved, thereby leading to a flawed healing response that could then contribute to adverse remodeling.

Individual differences in the inflammatory response, perhaps in part genetically, epigenetically, environmentally, or pathogenically modulated, may contribute to these deviations. Nonetheless, definitive proof of this concept is still lacking. The point remains, however, that identification of those patients who are at risk of adverse remodeling and identification of contributing mechanisms are critically important goals because progress in this area could result in markedly improved clinical outcomes. The same mechanistic information relating to adverse LV remodeling will also probably be relevant to the progressive adverse remodeling seen in patients with heart failure who do not have coronary artery disease and AMI. Thus, progress in this area has the potential for profound benefit in a broad array of patients with cardiovascular disease.

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