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Myocardial Remodeling: Cellular and Extracellular Events and Targets

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Abstract

The focus of this review is on translational studies utilizing large-animal models and clinical studies that provide fundamental insight into cellular and extracellular pathways contributing to post-myocardial infarction (MI) left ventricle (LV) remodeling. Specifically, both large-animal and clinical studies have examined the potential role of endogenous and exogenous stem cells to alter the course of LV remodeling. Interestingly, there have been alterations in LV remodeling with stem cell treatment despite a lack of long-term cell engraftment. The translation of the full potential of stem cell treatments to clinical studies has yet to be realized. The modulation of proteolytic pathways that contribute to the post-MI remodeling process has also been examined. On the basis of recent large-animal studies, there appears to be a relationship between stem cell treatment post-MI and the modification of proteolytic pathways, generating the hypothesis that stem cells leave an echo effect that moderates LV remodeling.

Keywords

matrix metalloproteinases; large-animal models; myocardial infarction

INTRODUCTION

Myocardial remodeling is a continuum of changes in the structure and function of the myocardium that commonly occur as a result of a pathological process. Adverse myocardial remodeling is associated with poor patient outcomes in the context of ischemic heart disease and/or myocardial infarction (MI), cardiac hypertrophy, and cardiomyopathic disease states (1–3). Although each of these diseases demonstrates a unique myocardial remodeling phenotype, commonalities exist with respect to the cellular and extracellular compartments. Specifically, with respect to the cellular compartment, remodeling processes can include hypertrophy, proliferation, apoptosis, necrosis, and autophagy (4–7). The extracellular compartment can undergo increased synthesis and accumulation, degradation, and changes in composition and structure (4, 8, 9). Although all cardiac disease states likely encompass each of these changes within the cellular and extracellular compartments, these events are likely to be disease specific with respect to magnitude, direction, regionality, and temporality. The net balance and timing of these cellular and extracellular events dictate the

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distinctly different myocardial phenotypes that arise from these disease processes. Accordingly, rather than examine each of these relevant disease states separately, this review focuses upon one area to identify new findings regarding cellular and extracellular processes that affect the myocardial remodeling process. For this purpose, this review focuses upon the area of ischemic heart disease, most notably ischemia-reperfusion and/or MI. Although significant insight and hypothesis generation regarding myocardial remodeling have been gained through the use of transgenic mouse models (10, 11), the physiological differences between the cardiovascular systems of rodents and large animals, with respect to left ventricular (LV) remodeling, are an important consideration. Therefore, translational studies utilizing large-animal models and clinical studies that provide fundamental insight into cellular and extracellular pathways contributing to post-MI remodeling are emphasized.

LEFT VENTRICULAR REMODELING AND STEM CELLS

Endogenous Stem Cell Activation/Mobilization

Following an MI, the resulting inflammatory state influences a cascade of cellular processes and signaling pathways, extending beyond the confines of the LV to the peripheral circulation. This systemic inflammatory state is an impetus for the spontaneous mobilization of bone marrow–derived cells (12–16), resulting in an influx of cells such as granulocytes, lymphocytes, and monocytes into the peripheral circulation (15). Along with these terminally differentiated cells, a small subpopulation of monopotential and multipotent cells, commonly referred to as bone marrow–derived stem cells, has been detected using flow cytometric analysis of peripheral blood samples taken from patients in the days following an MI (14). This finding was first described in a clinical study by Shintani et al. (17), who reported that CD34⁺ mononuclear cells, the putative precursor to endothelial progenitor cells, reach peak elevation at 7 days post-MI. Moreover, numerous associative clinical studies have detailed a temporal relationship between post-MI LV remodeling and the emergence of bone marrow–derived stem cells, as summarized in Figure 1 (12, 18–21).

In 2001 Orlic et al. (22) proposed that bone marrow–derived stem cells can differentiate into cardiac myocytes. Bone marrow cells injected adjacent to an MI in a mouse model generated *de novo* myocardium and improved cardiac function (22). This report was preceded by a study by the same laboratory group that stated that adult cardiac myocytes can divide and regenerate the human myocardium (23). Although further studies in a number of laboratories could not recapitulate these findings entirely (24, 25), these initial studies gave rise to the concept of tracking and regulating bone marrow–derived stem cells in the post-MI context (13, 26–30). Several studies utilized large-animal models of MI to demonstrate the ability to track bone marrow–derived stem cells (26, 28, 30). For example, Hill et al. (26) used magnetic resonance imaging to track iron-labeled, bone marrow–derived stem cells in post-MI pigs, detecting cell engraftment into the infarct region up to 21 days post-MI (Figure 2). These results indicated that *in vivo* study of the migration, retention, and engraftment patterns of bone marrow–derived stem cells was possible in the post-MI context.

Given that granulocyte colony–stimulating factor (G-CSF) is frequently utilized in clinical hematology, with exogenous forms commercially available and commonly used to treat myelodysplastic syndromes (31), it is well established as a mobilizing agent of bone marrow–derived stem cells into the peripheral bloodstream (27). Subsequently, both large-animal and clinical studies have shown that G-CSF is positively correlated with the successful mobilization of bone marrow–derived stem cells post-MI (13, 29), setting the stage for studies evaluating the effects of post-MI G-CSF treatment on fundamental determinants of LV remodeling. Norol et al. (29) described the modulation of bone marrow–derived stem cells post-MI in a baboon model. These investigators reported that

subcutaneous injections of G-CSF resulted in an increase from $5 \mu\text{l}^{-1}$ to $73 \mu\text{l}^{-1}$ CD34⁺ cells in the peripheral blood between days 8 and 12 post-G-CSF administration and improved infarct region myocardial blood flow at 4 weeks post-MI compared with control animals (29). In a porcine model, subcutaneous G-CSF treatment for 7 days post-MI reduced infarct size and improved LV function (32). This report heralded a large number of clinical trials examining the effects of pharmacological modulation of bone marrow–derived stem cells on indices of post-MI remodeling (18, 19, 33–37). On the basis of a small clinical trial in 2005, Kuethe et al. (19) reported that G-CSF treatment in 14 MI patients improved regional wall motion, perfusion, and LV ejection fraction compared with controls. In that same year, the results of a pilot clinical trial by Ince et al. (18) suggested that G-CSF treatment attenuated the post-MI LV remodeling process.

However, the promise of these early clinical trials was not borne out by several subsequent studies (33–37). The largest of these trials, the REVIVAL-2 study, examined the effects of G-CSF treatment on 56 patients with MI, reporting significant bone marrow–derived stem cell mobilization, as shown in Figure 3 (37). However, the study found that fundamental determinants of LV remodeling, such as LV end diastolic volume, were unaffected by G-CSF treatment at 5 months post-MI (37). Furthermore, a recent meta-analysis performed by the same authors found no significant beneficial effects of G-CSF treatment on post-MI remodeling (36). These disparate results led to a reexamination of the necessary quality, quantity, and localization of the bone marrow–derived stem cells mobilized post-MI with regard to influencing LV remodeling (38).

At present, the efficacy of G-CSF on LV remodeling continues to be controversial, as the two most recent clinical studies have again shown benefit with G-CSF treatment post-MI (20, 21). A study by Leone et al. (20) emphasized the need to select patients with an ejection fraction of less than 50% as a key criterion for the efficacy of G-CSF treatment. Preclinical studies have examined the effects of combinatorial treatments, proposing that the recruitment of bone marrow–derived stem cells by G-CSF alone is not effective but may be beneficial in combination with other hematopoietic factors (39). However, all these studies are predicated on the mobilization of endogenous bone marrow–derived stem cells. The manipulation of exogenous bone marrow–derived stem cells, as well as of other cell populations, is another alternative that has been explored in regard to the attenuation of LV remodeling.

Exogenous Stem Cell Delivery and Influence on Left Ventricular Remodeling

The pursuit to harness the potential benefits of stem cells in the post-MI context has included a number of different cell subpopulations and exogenous delivery routes. Cells derived from peripheral blood (40), umbilical cord blood (41, 42), and bone marrow (43, 44) have been explored with the goal of ameliorating the LV remodeling process. More recently, the myocardium has been recognized as a source of so-called cardiac progenitor cells (45–47). The bulk of large-animal and clinical trials have focused on autologous bone marrow–derived stem cells, given that they are relatively easily accessible and there is no concern of immune system rejection (48). The characterization of the specific cell subpopulations utilized from these sources has also varied among studies. Common cell surface antigenic markers used to identify the subpopulation of interest include CD34, CD45, CD133, c-kit, stem cell antigen-1, and the endothelial cell marker kinase domain receptor (KDR) (49, 50). Cell populations with a predominance of CD34 and CD133 positivity have been correlated with the potential for angiogenesis (51) and have therefore been especially prominent in the context of post-MI remodeling. The mode of cell isolation and/or expansion utilized by a study can also introduce variability into cells derived from a common lineage. Whereas some studies have utilized freshly isolated cells filtered via density gradient centrifugation/sedimentation, other studies have employed ex vivo culture–expanded cell populations in a

number of different media (52). Methods to deliver the cells to the myocardium have included intravenous infusion (53), intracoronary injection (53–55), transendocardial injection using catheter-based techniques (53–57), and percutaneous (58) or open-chest (59–61) direct intramyocardial injection. Given the prevalence of percutaneous coronary intervention in acute MI patients, catheter-based delivery methods have been frequently used in clinical trials. Although the exogenous application of stem cells in the post-MI context has been the subject of multiple reviews and editorials, this review focuses on those large-animal and clinical studies with the specific response variable of LV remodeling.

Table 1 summarizes the large-animal studies performed to date (53–68). Fuchs et al. (56) were the first to investigate the effects of bone marrow–derived stem cells delivered transendocardially on collateral flow and myocardial wall thickness. Pigs treated with bone marrow–derived cells 4 weeks post-MI had improved collateral flow and an approximately 50% increase in wall thickening of the ischemic lateral wall 4 weeks posttreatment compared with controls (56). A few large-animal studies have compared cell delivery methods and dosages in attempts to optimize the beneficial effects on LV remodeling. For example, Freyman et al. (53) compared intravenous, intracoronary, and transendocardial bone marrow–derived stem cell delivery in a pig MI model, reporting that, although the intracoronary route showed the most engraftment, it was also associated with a higher incidence of decreased coronary blood flow, highlighting an important safety issue to consider in clinical trials. Hamamoto et al. (60) examined the dose-dependent effects of bone marrow–derived stem cells on LV remodeling in a sheep model, reporting that lower cell doses resulted in decreased end diastolic volumes at 8 weeks post-MI compared with controls and sheep receiving higher cell doses. These results underscored both the difficulty of comparing results from clinical trials that used differing doses of cells and the need for comparative studies to determine the optimal cell dosage. In a different report, Dixon et al. (59) examined the effects of various concentrations of exogenously delivered bone marrow–derived stem cells on LV geometry in the post-MI context in sheep. Despite a lack of long-term cell engraftment with even the highest cell concentration treatment, the study reported a persistent decrease in LV dilation, especially with the delivery of lower cell concentrations (Figure 4) (59). These results suggest that there is a ceiling effect to the efficacy of increasing concentrations of bone marrow–derived cells delivered post-MI. Jameel et al. (61) recently studied the effect of bone marrow–derived stem cells on cardiac metabolism in pigs post-MI. At 16 weeks post-MI, the cell-treated animals had improved myocardial energetics and decreased LV end diastolic volume compared with controls (Figure 5) (61). Interestingly, the study found no significant cell engraftment at 16 weeks post-MI (61). In summation, these studies demonstrated that high concentrations and long-term engraftment of exogenously delivered cells were not required to affect LV remodeling. The persistence of alterations in LV geometry without evidence of long-term cell engraftment suggests that paracrine effects may be responsible for the effects of bone marrow–derived cells on LV remodeling. The mechanisms behind these effects remain to be established, requiring further studies on clinically relevant large-animal models.

Human Studies of Stem Cells in Relation to Left Ventricular Remodeling

The provocative results from early rodent studies supporting the regenerative capacity of stem cell treatment post-MI elicited great enthusiasm and sparked a rapid progression to human studies. Specifically, a study by Strauer et al. (69), which utilized intracoronary delivery of bone marrow–derived cells in a subset of post-MI patients, reported a 26% decreased perfusion defect and a trend toward decreased end diastolic volume with cell treatment compared with controls at 3 months follow-up. The larger, randomized clinical study TOPCARE-AMI by Assmus et al. (70) followed. This latter study reported that intracoronary delivery of peripheral blood–derived stem cells ($n = 30$) and bone marrow–

derived stem cells ($n = 29$) 5 days after MI reduced LV end systolic volume 4 months later and decreased infarct size at 12 months posttreatment in both groups (70). However, a report by Kuethe et al. (71) failed to find any improvement in LV function up to 12 months after intracoronary injection of bone marrow–derived stem cells in a study of 5 patients treated 6 days post-MI. These early studies often lacked appropriately matched control groups (71) and focused on the feasibility and safety of cell treatment rather than the endpoint of LV remodeling.

For the purpose of examining exogenous stem cell treatment in the context of LV remodeling, our discussion is limited to those studies that analyzed changes in myocardial structure and geometry in the post-MI period through measures of LV end diastolic volume and/or infarct wall thickness. Table 2 summarizes studies that have examined LV remodeling both short- and long-term post-MI (72–77). Results from these clinical studies have often been disparate. For example, the 5-year results of the BALANCE study of intracoronary delivery of bone marrow–derived stem cells post-MI reported a significant reduction in infarct size, suggestive of the reemergence of viable myocardium (77). This result harkens back to the early studies reporting the regenerative capacity of stem cells post-MI, which have yet to be substantiated. The BALANCE study also reported that the LV end diastolic volume in the control group increased 12 ml at a 5-year follow-up as opposed to a 7-ml increase in the treatment group (77). The clinical relevance of this result is debatable, and it conflicts with the findings of other studies. Specifically, the 5-year results from the BOOST clinical trial reported no significant difference at any time point in LV end diastolic volume between patients who underwent intracoronary delivery of bone marrow–derived stem cells post-MI compared with controls (78). Similarly, the 3-year follow-up results of the ASTAMI study of intracoronary delivery of bone marrow–derived stem cells reported no significant effect on LV end diastolic volume compared with controls (79). Ultimately, the discordant results of long-term studies may reflect a lack of uniformity in the preparation, characterization, and delivery methodology of cells between various reports. The present uncertainty that surrounds post-MI stem cell treatment is likely a product of the premature progression into human studies and underscores the need for preclinical studies to address key issues prior to the inception of clinical trials.

EXTRACELLULAR PROTEOLYTIC ENZYMES AND LEFT VENTRICULAR REMODELING POST–MYOCARDIAL INFARCTION

As detailed in the subsequent section, a number of cellular and extracellular factors contribute to the complex process of myocardial remodeling following MI. Specifically, targeting cellular events such as myocyte loss, growth, and differentiation were the impetus for research regarding the use of endogenous and exogenous stem cells. However, significant alterations in the structure and composition of the myocardial extracellular matrix (ECM) occur following MI (80–82). In the early period following a coronary artery occlusion with or without reperfusion, degradation of normal ECM occurs with invasion of inflammatory cells at the site of initial injury and the induction of bioactive peptides and cytokines. Through the use of large-animal models of MI and imaging methods such as magnetic resonance imaging, it is possible to identify early and definable changes in the myocardial ECM that are associated with changes in LV geometry (Figure 6) (83, 84). Thus, dynamic changes that directly affect the mechanical properties of the LV myocardium occur within the myocardial ECM in the initial and early phases of the post-MI period. The later phase of post-MI remodeling results in ECM changes within all regions of the LV: the MI region, the viable myocardium within the border zone, and the remote region. Within the MI region, the newly formed ECM is associated with persistent proteolysis and as a result forms a relatively unstable substrate that is highly susceptible to deformation from the intracavitary stresses generated during the cardiac cycle (85–88). This adverse remodeling process,

termed infarct expansion, occurs in the absence of additional myocyte injury or alterations in LV loading conditions (83, 89–92). This post-MI remodeling process is a clinically significant problem in that it can lead to LV dilation and dysfunction and the progression to heart failure. Indeed, this post-MI remodeling process, which includes changes in ECM structure and composition, is an independent predictor of morbidity and mortality (92). It has been postulated that an acceleration of ECM degradation occurs within the myocardium within and surrounding the MI (border zone) and facilitates the infarct expansion process in this later phase of post-MI remodeling. Although the molecular pathways that contribute to ECM remodeling post-MI are complex and multifactorial, the purpose of this review is to place a specific ECM proteolytic system in the context of post-MI remodeling, with particular focus on recent large-animal studies as well as the integration of stem cell studies.

The matrix metalloproteinases (MMPs) are among the large number of proteolytic enzymes that can contribute to ECM remodeling (93). The MMPs are a family of more than 25 species of zinc-dependent proteases that are essential for normal tissue remodeling in processes such as bone growth, wound healing, and reproduction (93). In general terms, MMPs are synthesized as inactive zymogens and are secreted into the extracellular space as proenzymes (pro-MMPs). The pro-MMP binds specific ECM proteins and remains enzymatically quiescent until the propeptide domain is cleaved. Although the MMPs were initially considered to be secreted in a soluble, proenzyme form, a unique subfamily of MMPs, the membrane-type MMPs (MT-MMPs), of which MT1-MMP is the best characterized, are fully active once inserted into the cell membrane (93). Thus, unlike the secretable MMPs, MT-MMPs are inserted into the cell membrane in an already activated form and can therefore serve as a localized, pericellular site of ECM proteolytic activity. A critical control point for MMP activity is through the inhibition of the activated enzyme by the action of a group of specific MMP inhibitors termed tissue inhibitors of matrix metalloproteinases (TIMPs). Of the four known TIMP species, TIMP-1 and TIMP-2 are the most studied. In general terms, TIMPs bind to the catalytic domain of active MMPs and thereby prevent access to substrates. Although the relative binding affinities of TIMPs to different active MMPs can depend upon assay conditions, it appears that TIMP-1 binds with less efficiency to MT-MMPs (94). TIMP-3 is unique among the known TIMPs in that it binds directly to ECM proteins and can thereby provide a means for stabilizing MMP-TIMP complexes within the interstitial space (95, 96). In TIMP-4, the most recently identified member of the TIMP family, a high degree of expression occurs within the cardiovascular system, most notably the myocardium (97, 98). Although new findings suggest that diverse biological roles of TIMPs likely exist with respect to modulating myocardial growth, viability, and function (99), these low-molecular-weight proteins compose an important endogenous system for regulating MMP activity in vivo. As a consequence, the TIMPs that are expressed in high abundance or with relative specificity to the myocardium directly affect MMP activity and subsequently the matrix remodeling process. This review examines recent human and large-animal studies with respect to the interrelationship between MMPs/TIMPs and LV remodeling post-MI.

In the context of clinical investigations, direct measurement of myocardial MMP/TIMP profiles is not feasible, and therefore peripheral blood sample measurements must necessarily serve as surrogate markers of MMP/TIMP induction post-MI. The advantage of this approach is that serial measurements are possible and can construct temporal profiles of MMPs/TIMPs post-MI. Indeed, numerous human studies have examined specific MMP and TIMP types in the post-MI context, including the collagenases MMP-1 and MMP-8, the gelatinases MMP-2 and MMP-9, the stromelysin and matrilysin MMP-3 and MMP-7, and the tissue inhibitor TIMP-1 (100–113). Soon after an MI (within the first 48 h), Inoue et al. (102) reported elevated levels of MMP-1. These same investigators measured MMP-1 levels in the coronary sinus and the aorta, demonstrating an increased release of MMP-1 from the

myocardium (102). Changes in MMP-2 plasma levels have been reported post-MI (103–113). However, a uniformity in the timeline of these changes remains to be established. In contrast, several studies have reported elevated plasma levels of MMP-9 in the days immediately following an MI (101, 103, 105, 109, 111–114). For example, Squire et al. (109) demonstrated that MMP-9 levels more than doubled between day 2 and day 4 post-MI. Moreover, a subset of studies have specifically investigated the relation of plasma MMP-9 levels post-MI to LV remodeling (112, 115). For example, Webb et al. (112) examined MMP/TIMP plasma profiles in post-MI patients and correlated elevated MMP-9 levels at day 5 post-MI with a threefold increase in LV end diastolic volume at 28 days post-MI (Figure 7). More recently, Kelly et al. (115) reported a 50% increase in plasma MMP-9 levels in patients with an increased LV end diastolic volume at 6 months post-MI compared with patients in whom LV end diastolic volume had decreased. Other characteristics of the post-MI plasma MMP profile include an elevation of MMP-3 and MMP-8 immediately following an MI (102). Elevated plasma levels of TIMP-1 have been reported for up to 6 months post-MI (112). Therefore, a temporal signature of MMPs and TIMPs has been developed and related to LV remodeling post-MI.

Due to the diversity of MMP and TIMP substrates and functions, a number of etiologies may account for the changes in the MMP/TIMP profile post-MI. A possible mechanistic explanation for the elevation of plasma MMP-9 post-MI is transcriptional regulation, as the MMP-9 promoter region contains transcription factor-binding domains that are responsive to cytokines elaborated in the early post-MI period (116). The localized recruitment and degranulation of neutrophils associated with the acute inflammatory cellular response to MI are other potential sources of elevated plasma MMP-9 as well as elevated plasma MMP-8 levels (112). The involvement of MMP-1 and MMP-3 in coronary artery plaque rupture associated with an MI is a potential etiology of elevated plasma levels of these MMPs (102, 117). Changes in plasma MMP/TIMP profiles post-MI have been demonstrated as prognostic tools. Specifically, studies have reported that plasma levels of MMP-9 and TIMP-1 correlate with echocardiographic findings of LV remodeling and are associated with cardiovascular risk factors (118–120). Currently, differing methodologies in sampling and analysis techniques among studies are a source of variability in MMP/TIMP measurements. The post-MI plasma MMP/TIMP portfolio likely holds great prognostic utility that will not be fully realized until methodological uniformity is achieved among studies. However, plasma profiles of MMPs and TIMPs are at best surrogate markers reflecting local myocardial levels and lack information regarding proteolytic potential and mechanistic cause-effect relationships in the post-MI context. Furthermore, the elucidation of cause-effect mechanistic relationships in post-MI MMP/TIMP profiles and LV remodeling has relied heavily upon large-animal studies.

LARGE-ANIMAL STUDIES AND MMP/TIMP PROFILES IN RELATION TO POST-MYOCARDIAL INFARCTION LEFT VENTRICULAR REMODELING

The remodeling processes that take place in each of the post-MI myocardial regions are unique. Heterogeneity in the remodeling process among the different myocardial regions has been correlated to heterogeneity in the MMP/TIMP profile post-MI (121, 122). Specifically, Wilson et al. (122) examined LV remodeling and MMP/TIMP profiles in sheep 8 weeks post-MI, demonstrating that changes in regional geometry were associated with changes in MMP/TIMP stoichiometry post-MI. For example, MMP-8, MMP-13, and MT1-MMP increased by more than 300% in the border zone and MI regions, whereas MMP-1 and MMP-9 were unchanged in the remote region and decreased in the border zone and MI regions. MMP-7 also decreased in the border zone and MI regions, whereas MMP-2 increased in these regions (122). In regard to the TIMPs, TIMP-4 fell by 50% in the MI region, whereas TIMP-1, TIMP-2, and TIMP-3 levels were undetectable within the MI

region (122). These results suggested that targeting the specific MMPs, which were induced locally within the post-MI myocardium, held therapeutic potential to attenuate LV remodeling. However, which specific MMP or TIMP types are causative agents in LV remodeling remains under debate and requires studies utilizing transgenic constructs and/or pharmacological MMP inhibition for further elucidation.

MODIFYING MMP ACTIVATION AND POST-MYOCARDIAL INFARCTION REMODELING

To investigate a potential cause-effect relationship between the post-MI MMP/TIMP profile and LV remodeling, studies utilizing large-animal models of MI and pharmacological MMP inhibition were undertaken (91, 123–125). Pharmacological development of compounds with significant potency across all MMP types, known as broad-spectrum MMP inhibitors, was initially aimed at connective tissue disorders such as arthritis. These compounds were then clinically evaluated in the context of severe gastrointestinal cancers (126). Subsequently, broad-spectrum MMP inhibitors that had potential indications in cardiovascular disease emerged. Mukherjee et al. (91) demonstrated a decrease in LV end diastolic volume and infarct expansion at 8 weeks post-MI in pigs receiving a broad-spectrum MMP inhibitor compared with controls. The study also found that specific MMP types were normalized in the MI region and that levels of TIMP-1 were increased with pharmacological MMP inhibition initiated at day 5 post-MI (91). These results helped provide proof of principle that MMP activation is likely causative of adverse remodeling post-MI. However, broad-spectrum MMP inhibition was not advanced to clinical studies because of a concern for systemic side effects (126). Therefore, pharmacokinetic studies were performed in a pig model, defining titration levels that would selectively spare certain MMPs (125). As a result, subsequent studies were undertaken using a MMP-1- and MMP-7-sparing MMP inhibitor approach (123, 124). For example, Morita et al. (124) reported that treatment with a MMP-1- and MMP-7-sparing MMP inhibitor resulted in significantly attenuated LV remodeling in dogs with ischemic cardiomyopathy. These results proved that it was not necessary to inhibit the entire myocardial MMP portfolio to influence LV remodeling. This particular compound advanced to an initial clinical study, wherein patients 48 ± 24 h post-MI were randomized to receive this specific MMP inhibitor or placebo for 90 days (127). The study reported a decrease in LV dilation post-MI in the MMP inhibition group, but this decrease did not reach statistical significance (127). The reasons for the lack of significant attenuation of LV remodeling in the MMP inhibitor group in this study are likely multifactorial. First, the clinical study instituted the sparing MMP inhibitor within 24 h of MI onset, as opposed to preclinical studies that began treatment at day 5 post-MI (91). Therefore, the initial wound-healing period post-MI may have been negatively influenced in the clinical study. Second, adequate drug dosing was likely not achieved in the clinical study after the dosing regimen was altered owing to concern over potential drug side effects (93). Furthermore, the pharmacodynamic profile established for this particular MMP inhibitor using large-animal models (125, 128) was not applied to this clinical study. As a consequence, the computed plasma concentrations achieved in the clinical study were fourfold lower than those reported to successfully modify post-MI remodeling in pigs. The equivocal results of the study subsequently dampened enthusiasm for further research in the field of targeting MMP inhibition in post-MI remodeling. This is an example of the significant chasm between basic translational research and advancements in clinical treatment (129). The issues articulated above in regard to the failure of translating results and lessons learned from large-animal studies to the clinical study highlights how vast and detrimental this chasm can be.

Other attempts to influence the post-MI MMP/TIMP profile have targeted upstream signaling pathways important in LV remodeling. One such bioactive molecule is angiotensin

II, which exacerbates acute ischemic injury and regulates ECM homeostasis in the myocardium (130). Specifically, Jugdutt et al. (131) recently investigated the influence of an angiotensin II type I receptor blocker on MMP-2 and MMP-9 levels in a canine model of ischemia-reperfusion. The study demonstrated reduced levels of MMP-2 and MMP-9 following treatment with the angiotensin II type I receptor blocker during reperfusion (131). This finding was associated with reduced LV dilation following reperfusion (131). Another bioactive molecule that has been associated with induction of certain MMP types is endothelin. Endothelin receptor antagonism has been studied in a pig model of ischemia-reperfusion and is reported to decrease MT1-MMP activity (132). Aging is another factor that may be an exacerbating factor in LV remodeling post-MI (130). Elevated MMP-2 and MMP-9 levels, along with altered ratios of MMP-9 to TIMP-3 and MMP-2 to TIMP-1, have been demonstrated with age in a canine model of ischemia-reperfusion and may contribute to more severe early LV remodeling (133). Thus, signaling pathways and factors with upstream influences on the MMP/TIMP profile post-MI are potential targets to attenuate LV remodeling.

EXOGENOUS STEM CELL THERAPIES AND MMP/TIMP PROFILES

As discussed above, the potential therapeutic effects of exogenously delivered stem cells have been explored in the context of post-MI LV remodeling. Results from small-animal studies showed promise for stem cell delivery to influence the post-MI MMP/TIMP portfolio (134, 135). These initial small-animal studies have now been advanced to large-animal models that examine the effects of stem cells on the post-MI MMP/TIMP profile and LV remodeling (59, 136). For example, the delivery of bone marrow–derived mesenchymal precursor cells to the border zone myocardium immediately following MI was evaluated in a sheep model (59). This study demonstrated altered MMP/TIMP stoichiometry at 8 weeks post-MI, which correlated with reduced LV dilation (59). Specifically, stem cell treatment resulted in decreased MMP-7 and MMP-13 levels and normalized MT1-MMP levels in the border zone region compared with MI-only sheep. As shown in Figure 4, despite the lack of cell engraftment at 8 weeks post-MI, modification of proteolytic pathways (i.e., collagen degradation) and an influence on LV remodeling were evident. Another large-animal study suggested that intracoronary injection of mesenchymal stem cells 3 to 7 days post-MI in pigs resulted in altered MMP/TIMP profiles post-MI (136). Taken together, these results suggest that the altered course of LV remodeling in the absence of long-term cell engraftment is due to paracrine effects from stem cells, as illustrated in Figure 8.

CONCLUSION

The important concept from these new observations is that stem cell treatments post-MI without long-term engraftment can modify proteolytic profiles that can alter post-MI remodeling. This opens the possibility that long-term cell engraftment is not a requirement to modify endogenous systems that cause adverse post-MI remodeling. Although this scenario remains speculative, Figure 8 illustrates this postulate, whereby enhanced proteolytic pathways occur post-MI and an echo effect of the delivered stem cells occurs, attenuating this process. Recognition that stem cell therapy interacts with alternative biological pathways moves us beyond the canonical belief that the use of stem cells is effective on post-MI remodeling only when transformation to cardiac-type cells occurs or when long-term engraftment is achieved (22, 47, 64, 84).

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Figure 1.

Mobilization of endogenous endothelial progenitor cells post–myocardial infarction (MI) in relation to the time course of left ventricular (LV) remodeling. The level of CD34⁺ cells in the peripheral blood peaks at 7 days post-MI, whereas LV dilation peaks at 90 days post-MI. WBCs, white blood cells. Data extrapolated from References 17 and 112.

Figure 2. Serial in vivo and ex vivo magnetic resonance imaging tracking stem cells. (*a–c*) Serial short-axis views of diastolic frames demonstrate a persistent signal void following injection of iron-labeled mesenchymal stem cells in post-myocardial infarction (MI) pigs on (*a*) day 1, (*b*) day 4, and (*c*) day 21. (*d*) Corresponding view of explanted heart on high-resolution 3D magnetic resonance imaging showing a signal void indicative of iron-labeled cells. Reproduced from Reference 26.

Figure 3.

CD34⁺ cell levels on day 5 of granulocyte colony-stimulating factor (G-CSF) versus placebo treatment, and left ventricular (LV) end diastolic volume (EDV) index and LV ejection fraction (EF) at 4–6 months post-myocardial infarction (MI) in the REVIVAL-2 study. Although subcutaneous G-CSF treatment post-MI significantly mobilized CD34⁺ cells, it did not influence LV remodeling. Data are presented as mean $\pm$ standard deviation. The asterisk denotes $p < 0.05$ for the G-CSF group versus the placebo group. Sample sizes are as follows: G-CSF, $n = 56$; placebo, $n = 58$. Created from Reference 37.

Figure 4.

Exogenous stem cell treatment and post-myocardial infarction (MI) remodeling. (a) Parallel left ventricular (LV) sections obtained from the MI border zone, stained with hematoxylin (H) and eosin (E) and for the Y chromosome, were obtained at 1 h post-MI induction and cell injection (225 M), as well as at 8 weeks post-MI whereby increasing concentrations of cells were injected in female sheep. Sections from testis as a positive control for the Y chromosome (cells harvested from male sheep) as well as referent normal sheep myocardium were included in this analysis. A strong basophilic linear array of cells was readily evident within the targeted injection site at 1 h following mesenchymal precursor cell (MPC) injection (*arrows*). At 8 weeks post-MI, a pleomorphic staining pattern was observed within the border zone that included residual myocytes, inflammatory cells, myofibroblasts, and bands of fibrillar collagen. Immunolocalization for the Y chromosome revealed a strong positive signal in the testis and in the linear array of cells within the injection site at 1 h. The positive Y chromosome staining is therefore reflective of successful implantation of the cells within the border zone post-MI. However, examination at 8 weeks post-MI revealed an absence of Y chromosome staining indicative of a failure of long-term engraftment. Treatment groups are labeled as follows: normal = referent control ($n = 6$), MI only = cell medium only ($n = 14$), 25 M = 25×10^6 MPCs ($n = 7$), 75 M = 75×10^6 MPCs ($n = 7$), 225 M = 225×10^6 MPCs ($n = 10$), 450 M = 450×10^6 MPCs ($n = 8$). Scale bar = 200 μ m. (b) LV end diastolic volume (EDV) and collagen degradation [as measured by plasma ICTP (carboxy-terminal telopeptide of type-1 collagen) levels] at 8 weeks post-MI, with and without cell treatment. Decreased LV dilation was demonstrated in the lower concentration cell groups, whereas collagen degradation was increased in the 25-M group. Treatment groups are labeled as in panel *a*. Values are presented as mean $\pm$ SEM (standard error of the mean). The asterisk denotes $p < 0.05$ versus control, § denotes $p < 0.05$ versus MI only, and # denotes $p < 0.05$ versus 25 M. Reproduced from Reference 59.

Figure 5.

Effect of bone marrow–derived multipotent progenitor cell transplantation on myocardial energetics at 4 months post–myocardial infarction (MI). Myocardial high-energy phosphate and Pi levels are reflected by the creatine phosphate (PCr):ATP ratio at baseline and under increased workload [dobutamine and dopamine (Db + Dp)]. The subendocardial and subepicardial PCr:ATP ratios were significantly higher in pigs treated with cells (MI + cells) compared with those without treatment (MI). After increased workload the PCr:ATP ratio decreased in both groups but was higher in the cell treatment group. Values are presented as mean $\pm$ standard deviation. The asterisk denotes $p < 0.05$ versus MI, and ‡ denotes $p < 0.05$ versus baseline. Adapted from Reference 61.

Figure 6.

Delayed-contrast magnetic resonance images from a nonreperfused pig myocardial infarction (MI). Top row: 4 h after occlusion. Middle row: 24 h after occlusion. Bottom row: 8 days after occlusion. First column: images acquired 2 min after contrast injection. Second column: images acquired 12 min after contrast injection. Third column: images acquired 22 min after contrast injection. Fourth column: images acquired 32 min after contrast injection. Hyperenhancement of the MI is seen at and beyond 24 h post-MI and at 12 min or later following contrast injection. The spatial extent of the hyperenhancement increased from the MI to the border zone region and became transmural at 8 days post-MI. Reproduced from Reference 84.

Figure 7.

Left ventricular (LV) remodeling post-myocardial infarction (MI) in relation to temporal plasma matrix metalloproteinase (MMP) profile. (a) LV end diastolic volume increased from reference control subjects at post-MI day 1 and remained elevated. Asterisk denotes $p < 0.05$ versus reference controls. (b) MMP-9 levels remained elevated throughout the post-MI period. The asterisk denotes $p < 0.05$ versus normal reference range. Adapted from Reference 112.

Figure 8.

Effects of stem cells on post-myocardial infarction (MI) left ventricular (LV) remodeling. (a) Post-MI, several proteolytic pathways contribute to adverse LV remodeling. This includes the induction of proteases such as matrix metalloproteinase (MMP)-2, MMP-9, and MT1-MMP (membrane-type 1 MMP), which are active in remodeling the myocardial matrix. (b) Stem cell injection and loss. The exogenous delivery of various types of stem cells was performed in attempts to alter the LV remodeling process. Over time, the stem cells are lost from the matrix, and long-term cell engraftment is not achieved. (c) Post-stem cells/post-MI. Although the stem cells are no longer present, they leave behind an echo effect that alters the proteolytic pathways. Here, decreased activation of MMPs leads to increased stability in the matrix and therefore alters LV remodeling.

Table 1
Stem cell studies in large-animal models (listed in approximate chronological order)^a

Reference	Groups	Cell type	Cell count	Timing post-MI	Follow-up	Primary end point	Result
56	Pigs; TE (<i>n</i> = 7) versus placebo (<i>n</i> = 7)	BM	Unreported	4 weeks	4 weeks	Collateral perfusion, wall thickness	Improved collateral flow, wall thickness
62	Pigs; IM (<i>n</i> = 7) versus placebo (<i>n</i> = 5)	BM	6.0×10^7	2 weeks	4 weeks	Systolic wall thickening	Improved regional wall motion
63	Dogs; IM (<i>n</i> = 6) versus placebo (<i>n</i> = 6)	BM	100×10^6	4 weeks	8 weeks	LV EF by echo	Improved EF
58	Pigs; IM (<i>n</i> = 7) versus placebo (<i>n</i> = 7)	BM	2×10^8	3 days	8 weeks	Infarct size	Decreased infarct size
53	Pigs; intravenous, IC, TE (<i>n</i> = 6 each)	BM	50×10^6	1 h	2 weeks	Engraftment	IC best engraftment
64	Pigs; IM (<i>n</i> = 7) versus placebo (<i>n</i> = 7)	BM	1×10^8	1 h	3 weeks	LV EF	Improved EF
54	Pigs; IC (<i>n</i> = 6) versus placebo (<i>n</i> = 6)	UCB	1×10^8	1 week	4 weeks	LV EDV, EF	No significant difference
55	Pigs; IC; adipose cells (<i>n</i> = 7), BM (<i>n</i> = 7)	AD BM	2×10^6	1 h	4 weeks	LV EF, perfusion defect	Equal improvement in AD or BM versus control
57	Dogs; TE (<i>n</i> = 6), IC (<i>n</i> = 7), control (<i>n</i> = 6)	BM	100×10^6	1 week	3 weeks	LV EF by echo	+13% in TE versus control
65	Pigs; IC (<i>n</i> = 7) versus placebo (<i>n</i> = 7)	BM	10×10^8	4 days	6 weeks	LV EF by MRI, infarct size	No effect
66	Pigs; IM low dose (<i>n</i> = 3) and high dose (<i>n</i> = 6)	BM	20×10^6 or 200×10^6	4 months	12 weeks	Infarct size by MRI	Decreased infarct size in high-dose group
67	Sheep; IM (<i>n</i> = 6) versus control (<i>n</i> = 3)	BM	1×10^5 – 1×10^6	3 weeks	12 weeks	LV EF by echo	Marginal improvement
60	Sheep; IM; four dosage groups	BM	25×10^6 , 75×10^6 , 225×10^6 , or 450×10^6	1 h	8 weeks	LV EF by echo	Improved EF
68	Pigs; IC; CDC (<i>n</i> = 7) versus placebo (<i>n</i> = 7)	CDC	1×10^7	4 weeks	8 weeks	Infarct size by MRI	Decreased infarct size in CDC group
59	Sheep; IM; four dosage groups	BM	25×10^6 , 75×10^6 , 225×10^6 , or 450×10^6	1 h	8 weeks	LV EDV, EF, MMP/TIMP profile, collagen	Attenuated remodeling at lower doses
61	Pigs; IM (<i>n</i> = 7) versus placebo (<i>n</i> = 7)	BM	50×10^6	1 h	16 weeks	Bioenergetic profile, LV EDV	Improved bioenergetics, decreased LV EDV

^a AD, adipose tissue; BM, bone marrow; CDC, cardiosphere-derived cells; EDV, end diastolic volume; EF, ejection fraction; IC, intracoronary; IM, intramyocardial; LV, left ventricular; MI, myocardial infarction; MMP, matrix metalloproteinase; MRI, magnetic resonance imaging; TE, transendocardial; TIMP, tissue inhibitor of matrix metalloproteinases; UCB, umbilical cord blood.

Table 2

Effects of bone marrow–derived stem cells on left ventricular end diastolic volume in clinical studies: short- and long-term results^a

Reference	Short term (<6 months)	Long term (>6 months)
69	↓	
70	↓	
72	↓	
73	↔	↔
74	↓	
75	↔	
76	↔	↔
77	↓	↓

^aDown arrows indicate decreased left ventricular end diastolic volume, and horizontal arrows indicate no change in left ventricular end diastolic volume.