Cell Therapy Limits Myofibroblast Differentiation and Structural Cardiac Remodeling

Basic Fibroblast Growth Factor-Mediated Paracrine Mechanism

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Background—Experimental cell therapy attenuates maladaptive cardiac remodeling and improves heart function. Paracrine mechanisms have been proposed. The effect of cell therapy on post infarction cardiac fibroblast and extracellular matrix (ECM) regulation was examined.

Methods and Results—Vascular smooth muscle cells (VSMC) were injected into the border zone of subacute infarcted syngeneic Fischer rat hearts and compared with medium-injected controls. Twelve weeks post injection, cell-treated hearts showed preserved ECM content and attenuated structural chamber remodeling. Myofibroblast activation (α-smooth muscle actin expression) was decreased significantly, while basic fibroblast growth factor (bFGF) expression, a known inhibitor of transforming growth factor β-1–induced fibroblast differentiation, was increased. Matrix metalloproteinase-2 expression and activation by gelatin zymography was unchanged between groups, while its endogenous inhibitor, tissue inhibitors of matrix metalloproteinase (TIMP)-2, showed both increased expression and enhanced inhibitory capacity in cell-treated hearts. To define paracrine mechanisms, in vitro effects of VSMC conditioned media on myofibroblast activation were assessed by 3-D collagen gel contraction assay. VSMC conditioned media significantly inhibited collagen contraction, while a specific bFGF inhibitor abolished this paracrine response. TIMP-2 induced collagen contraction, but the effect was suppressed in the presence of bFGF.

Conclusions—Extracellular matrix dysregulation post myocardial infarction is improved by cell therapy. These data suggest that cell transplantation attenuates myofibroblast activation and subsequent maladaptive structural chamber remodeling through paracrine mechanisms involving bFGF and TIMP-2. (Circ Heart Fail. 2012;5:349-356.)

Key Words: extracellular matrix — myofibroblasts — paracrine — remodeling

Structural ventricular remodeling influences the clinical progression of heart failure and has emerged as an important target for the development of novel medical and surgical therapeutic strategies.1 Cell transplantation is an innovative biological therapy that alters the structural remodeling response in failing hearts.2 Beneficial effects on heart structure and function have been observed in the absence of significant post transplant cellular retention and regeneration.2 To optimize this emerging therapy, our research efforts currently are focused on determining the cellular and molecular mechanisms responsible for the beneficial effects of cell therapy on reversing maladaptive structural remodeling.

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Extracellular matrix (ECM) responds to myocardial infarction (MI) by altering its abundance, composition, and spatial organization, with profound consequences on chamber structure and function.3 ECM homeostasis largely is determined by the balance between proteolytic enzymes (ie, the matrix metalloproteinase [MMPs]) and their highly regulated, multifunctional, endogenous inhibitors (ie, the tissue inhibitors of matrix metalloproteinase [TIMPs]). The balance of MMP and TIMP expression after MI is regulated within distinct spatial and temporal windows.4,5 As compared with remote myocardial regions, ECM dysregulation is persistent in the infarction border region (border zone) during both early and late phases of remodeling.5 Ongoing and excessive MMP activity in the late remodeling phase (8 weeks and later) is associated with ECM turnover, left ventricular (LV) dilatation, and a transition to decompensation.5,6 Activation of MMP-2 is a particularly potent stimulus for profound structural remodeling and the transition to heart failure,7 and similarly, deficient TIMP-2 can induce maladaptive post MI structural remodeling.8 Accordingly, the balance of MMP-2/TIMP-2 expression plays a critical role in myocardial remodeling.

Cardiac fibroblasts are the cell type primarily responsible for ECM regulation.9 After MI, increased transforming growth factor β-1 (TGF/β1) and other profibrotic cytokines
induce normally quiescent fibroblasts to convert to an invasive myofibroblast phenotype.10 When activated, cardiac myofibroblasts secrete MMPs to increase ECM turnover, followed by excessive ECM replacement (interstitial fibrosis).11,12 Ongoing myofibroblast-mediated ECM dysregulation results in myocardial fibrosis and progressive LV dilatation and systolic dysfunction.9

The role of ECM in the myocardial response to cell therapy has been defined poorly. Cell transplantation may limit maladaptive ventricular remodeling through multiple synergistic paracrine mechanisms.12 Some of the paracrine factors released by transplanted cells may influence ECM regulation.13 Vascular smooth muscle cells (VSMC) are capable of influencing ECM homeostasis through paracrine mechanisms.14 In addition, VSMC are incapable of substantial regeneration or development of synchronous contractile forces after cell transplantation into myocardium. We previously determined that VSMC transplantation reduced left ventricular dilatation and improved heart function in rodent models of cardiac injury.15,17 We hypothesized that post MI cell therapy prevents ECM dysregulation through paracrine signals, and in so doing, limits maladaptive remodeling. In this study we examined the influence of VSMC transplantation on ECM regulation during post MI structural remodeling in the rat heart. In addition, we explored the roles of basic fibroblast growth factor (bFGF) and TIMP-2 as possible paracrine molecular regulators of this remodeling response.

Methods

Experimental Animals

The experimental protocol was approved by the Institutional Animal Care Committee, and all procedures were performed according to the “Guide to the Care and Use of Experimental Animals” of the Canadian Council on Animal Care, and the “Guide for the Care and Use of Laboratory Animals” (The National Academy Press, revised 1996). Adult male Fischer rats weighing 170 to 200 g were obtained from Charles River Canada Inc. Green fluorescent protein (GFP) transgenic rats (University of Missouri) were obtained and used for cell tracking in a limited number of animals (n=3).

Cell Isolation and Expansion

Fischer rats (N=8) were euthanized and the aortas were harvested and enzymatically dissociated as previously described.9 Cells were plated in complete medium composed of Iscove’s modified Dulbecco’s medium supplemented with 10% fetal bovine serum and cultured in an incubator at 37°C with a 5% CO2 atmosphere. Cultured cells were characterized as VSMC immunohistochemically using an antibody against alpha smooth muscle actin (Sigma, Canada). VSMC (4×103) between passages 1 to 4 were suspended in 200 µL of serum-free medium. Similarly, VSMC cells from EGFP rats (n=3) were isolated, cultured, and characterized, and injected to assess cell engraftment.

Experimental Myocardial Infarction and Cell Transplantation

Coronary ligation to induce myocardial infarction in rats was performed as previously described.18 Echocardiograms were recorded using a Sonos S550 echocardiographic system and 12 MHz pediatric transducer (Agilent Technologies) to confirm significant infarction prior to cell transplantation. Animals with an LV ejection fraction >50% were eliminated. Two weeks after MI (reflecting a clinically relevant therapeutic window), hearts were exposed via the previous left thoracotomy incision. The infarcted zone was identified visually by its pale color and relative akinesis. VSMC were injected into the border zone of rat hearts (n=24), and volume-matched serum free medium was injected into hearts of control rats (n=24). The border zone was identified as a transition region between the akinetic anterior region and the lateral contractile region of the left ventricle. Four animals (n=4) were injected with GFP labeled cells for assessment of cell engraftment. Animals were euthanized 3 days after transplantation. Hearts were rinsed in saline. Specimens of the border zone of the LV infarction were collected and either fixed in buffered 10% formalin and embedded in paraffin, or frozen in optimal cutting temperature (Tissue-Tek). Frozen specimens for enzyme analysis and western blotting were stored at −80°C until use.

Immunohistochemistry and Histology

Frozen sections (5–7 µm) were fixed in cold methanol for 10 minutes, blocked in blocking buffer with 2% goat serum for 1 hour at room temperature (RT), and incubated in the primary antibody (mouse anti-α-smooth muscle actin [α-SMA]) at 1:500 [Sigma-Aldrich], rabbit anti-bFGF at 1:100, rabbit anti-TGFβ1 at 1:100, and rabbit anti-TIMP-2 [Santa Cruz Biotechnology Inc.] at 4°C overnight. Slides were incubated with secondary antibody, either Alexa Fluor Li-Cor (green) or Alexa Fluor 568 (red), at a dilution of 1:500 for 1 hour at RT, prior to mounting in Prolong Gold Antifade Reagent (Invitrogen) containing 4’,6-diamidino-2-phenylindole (DAPI) for counterstaining of nuclear visualization. All fluorescent images were captured using confocal laser scanning microscopy (LSM 5, Carl Zeiss) and analyzed using Zen software. Light microscopic images of paraffin fixed specimens were observed using a Zeiss Axiowert 40C microscope (Carl Zeiss). To quantitatively assess the number of cells expressing α-SMA (myofibroblasts), α-SMA positive cells were counted manually from 8 random fields from the border zone in each specimen (n=3 per group), averaged, and expressed as a percentage of the total number of cells. Additional samples (n=4 per group) underwent picrosirus red staining for myocardial collagen as described previously.16

Western Blotting

Samples were pulverized in liquid nitrogen using a Micro-Dismembrator (B Braun Biotech International GmbH) and extracted in ice cold extraction buffer (0.05 mol/L Tris-HCl, pH 7.4, 0.5% Triton X-100, 0.3 mol/L NaCl, 0.1% sodium dodecyl sulfate (SDS) and phenylmethanesulfonylfluoride (PMSF)). After 1 hour, homogenates were centrifuged (4°C, 20 minutes, 13 000 rpm), and the supernatant was collected and assayed for protein concentration using the bicinchoninic acid (BCA) protein assay kit (Thermo Scientific). Samples were stored in −80°C until use.

Matrix Metalloproteinase-2 Activity Assays

Samples were pulverized in liquid nitrogen using a Micro-Dismembrator (B Braun Biotech International GmbH) and extracted in ice cold extraction buffer (500 mmol/L Tris-HCl, pH 7.4, 200 mmol/L NaCl, 10 mmol/L CaCl2). After centrifugation, the supernatant was collected and stored at −80 °C until needed for

ELISA

Quantitative analysis of bFGF expression was measured using a human bFGF ELISA kit (RayBiotech, Inc.) according to the manufacturer’s instructions.

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MMP-2 activity and inhibition assay. Recombinant human MMP-2 protein was used as a positive control. The supernatant containing 30 μg of protein was mixed with 4x gel-loading buffer and separated by 10% SDS-PAGE containing 1 mg/mL gelatin, followed by incubation overnight at RT in renaturing buffer (2.5% Triton) with gentle shaking. Gels were developed overnight at RT in developing buffer, 50 mmol/L Tris-HCl, pH 8.0, 5 mmol/L CaCl₂, 1 μmol/L ZnCl₂, and stained with 0.25% Coomassie Blue and destained with methanol:glacial acetic acid: water (30:10:60). Zymograms were scanned using Odyssey Infrared Imaging System (LI-COR Biosciences).

Matrix Metalloproteinase-2 Inhibition Assay
The quenched fluorescence MMP assay was used to measure the activity of MMP-2 and the inhibitory capacity of myocardial border zone extracts. Briefly, to measure the activity, extracts containing 50 μg of protein were added to individual wells of a 96-well black plate in duplicate, combined with a MMP-2 fluorogenic substrate (10 μmol/L, Calbiochem) in each well. When cleaved by active MMP-2, the quenched fluorescence is emitted and the change in fluorescence over time was monitored for 30 minutes using the HTG-700 Bioassay Reader (PerkinElmer Life Sciences). The slope of the curve reflected MMP activity such that higher activity resulted in a greater slope. An MMP-2 standard was run on the same plate for each experiment. To measure MMP-2 inhibition, tissue extracts from the border zone region of each group were added to 20 ng of activated MMP-2 (20 μL). 4-aminophenyl mercuric acetate was used to activate pro-MMP-2. Recombinant human TIMP-2 (20 ng) was used as a positive control for inhibitory effect. Plates were incubated at RT for 30 minutes before substrate was added, and then plates were monitored to establish a time dependent MMP-2 activity curve. The inverse relationship between the inhibitory activity and the slope was calculated (whereby slope is inversely proportional to MMP inhibition).

Collagen Gel Contraction Assay
Cardiac fibroblasts were isolated from adult Fischer rats. Briefly, rat ventricular tissue was minced and digested in a digestion buffer (0.2% Collagenase II) for 5 minutes at 37°C in a water bath with gentle shaking. The cell suspension then was collected. This procedure was repeated up to 3 times. After centrifugation at 1200 rpm for 3 minutes at RT, the cell pellet was resuspended in IMDM medium containing 10% fetal bovine serum (FBS), and the isolated cells were plated and cultured for 5 to 6 days. Cardiac fibroblasts were trypsinized and counted. 400 μL of neutralized rat-tail type I collagen (BD Biosciences) mixed with cardiac fibroblasts in suspension was loaded into each well of a 24-well plate. Immediately after gel polymerization, 500 μL IMDM medium containing 1% FBS, either with TGFβ1 (0.2 ng/mL or 0.5 ng/mL), TGFβ1+bFGF (5 ng/mL), TGFβ1+bFGF+βFGF inhibitory peptide (βFGFi), VSMC conditioned medium+TGFβ1, and VSMC conditioned medium+TGFβ1+βFGFi. For inhibition of bFGF, experiments were performed using a commercially available inhibitory biopeptide (#61069, AnaSpec Inc). βFGFi doses were increased by a factor of 10 to examine a dose-response relationship (0-1000 μmol/L, 0-1000 μmol/L). The plate was incubated at 37°C for 24 hours. To initiate gel contraction, the gels were released with a spatula from the wells until they floated in the medium. An image was taken at serial time points, and Image J analysis software (NIH) was used to measure the area of contraction for up to 48 hours after initial release.

Left Ventricular Capacitance
The left ventricular passive pressure-volume relationship was determined as a measure of left ventricular chamber size. Passive diastolic pressure-volume curves were obtained in explanted hearts as previously described.19

Statistical Analysis
All group data are expressed as mean±SD. Statistical significance between groups was determined by Student’s t-tests, 1-way ANOVA, or 2-way repeated measures ANOVA as appropriate, followed by Student-Newman-Keuls multiple comparison post hoc analyses using GraphPad Prism (GraphPad Software) statistical analysis software, with P<0.05 considered statistically significant.

Results
Vascular Smooth Muscle Cells Engraftment
To establish engraftment in host myocardium for VSMC transplantation, donor VSMC were isolated from GFP rats and then injected 2 weeks after MI and euthanized after 72 hours. Confocal microscopic analysis and DAPI staining revealed limited GFP positive cells in the area of the cell injection (Figure 1A), with substantial cell fragmentation suggestive of necrosis and poor cell viability. These results confirm that VSMC cells were delivered successfully to the border zone region.

Myocardial Collagen Content
Picrosirius red staining for myocardial collagen was assessed and compared in the scar, border zone, and remote regions. Picrosirius red staining was enhanced in the scar and border zone regions as compared with normal animals without infarction (Figure 1B). There were no visible differences in collagen matrix content or distribution between VSMC-treated animals and controls in these regions. However, there was an obvious loss of perimysial collagen content in the remote myocardium of infarcted animals as compared with
normal controls, suggesting altered ECM homeostasis. Remote from the infarct area, collagen content and architecture was better preserved in the VSMC group, as compared with controls (Figure 1B, lower panel).

**Left Ventricular Size and Function**

The left ventricular pressure-volume relationship of cell treated hearts was left-shifted as compared with control hearts (Figure 2A), indicating smaller LV volumes and attenuated structural remodeling at 8 weeks post MI (group effect, \( P < 0.04 \)). By serial echocardiography, LV systolic function was better preserved after myocardial infarction in the VSMC group as compared with controls (\( P < 0.05 \) at 12 weeks, Figure 2B).

**Myofibroblast Activation**

Cardiac myofibroblasts mediate infarct repair and ECM production (fibrosis) during the process of post MI remodeling.11 To determine the extent of myofibroblast activation, \( \alpha \)-SMA expression (phenotypic marker for myofibroblasts) was determined by Western blotting. Expression of \( \alpha \)-SMA in cell-treated hearts was reduced significantly as compared with controls (Figure 3A). Quantitative analysis determined that \( \alpha \)-SMA expression of cell-treated hearts was 47 ± 28% of controls (n = 16 per group, \( P = 0.01 \)). Expression of \( \alpha \)-SMA is characteristic of smooth muscle cells in blood vessels in addition to myocardial myofibroblasts. Myocardial \( \alpha \)-SMA positive cells remote from vascular structures were significantly reduced in VSMC hearts (Figure 3B). Confocal imaging determined that the observed \( \alpha \)-SMA expressing cells were indeed remote from vascular structures and consistent with myofibroblasts (Figure 3C).

**Fibroblast Regulation by Growth Factors**

After MI, elevated TGF\( \beta 1 \) expression stimulates cardiac fibroblast differentiation to myofibroblasts, inducing wound contraction.11 VSMC transplantation did not alter TGF\( \beta 1 \) expression in the post MI remodeling heart as compared with controls (Figure 4A). The stimulatory effects of TGF\( \beta 1 \) on fibroblast differentiation are suppressed by simultaneous exposure to bFGF.20,21 We observed increased expression of bFGF after VSMC transplantation as compared with controls (Figure 4A). This observation was confirmed using a quantitative ELISA technique (Figure 4B). By confocal microscopy of the border zone region, we observed significant elevations of myocardial bFGF expressing cells in the interstitium of the VSMC group as compared with controls (Figure 4C).

**Extracellular Matrix Regulation**

Extracellular matrix dysregulation after myocardial infarction is characterized by increased matrix turnover through elevated proteolysis from excessive MMP activity, and reduced inhibition by TIMPs.3 We examined the MMP-2/TIMP-2 axis, given that MMP-2 constitutively is expressed by cardiac fibroblasts, and TIMP-2 serves as its primary endogenous inhibitor. Myocardial MMP-2 expression and activity was
assessed by gelatin zymography. MMP-2 activity and expression (pro and active forms) were not significantly different between groups (Figure 5A). We then measured MMP-2 inhibition by comparing VSMC myocardial extracts to control extracts in a quenched MMP florescence assay. The myocardial capacity for MMP-2 inhibition was increased in VSMC hearts (Figures 5B and 5C). In support of these data, protein expression of TIMP-2 was increased 3-fold in cell transplanted myocardium. N = 8 per group. C, Representative confocal micrographs of bFGF expression (red) in myocardium 72 hours after cell transplantation. VSMC indicates vascular smooth muscle cell transplanted group; CON, medium-injected control group; bFGF, basic fibroblast growth factor; TGFβ1, transforming growth factor β-1; *P < 0.01; blue, DAPI stained nuclei.

Discussion

Cell transplantation limits post MI maladaptive structural remodeling, even in the absence of myocardial regeneration or cell contraction.2 Remarkably, beneficial effects on heart structure and function have been observed consistently despite limited donor cell retention and unstable engraftment in the hostile host myocardial milieu.23 Smooth muscle cell transplantation, as performed in this study, previously has been shown to improve heart function and limit LV dilatation, despite limited engraftment.15,17,23 The mechanism of benefit is unclear. Paracrine mechanisms, primarily those that stimulate angiogenesis, have been proposed.12,13 In addition to well-established mechanisms such as angiogenesis, we suggest that cell therapy may provide additional beneficial effects on structural remodeling through ECM-dependent paracrine mechanisms.

We previously documented altered ECM regulation after VSMC transplantation in nonischemic cardiomyopathic hamsters in association with attenuated maladaptive chamber remodeling.16 In the current study, we focused efforts on post MI remodeling given its clinical importance and increased complexity as a remodeling phenomenon. Consistent with prior studies,15,23 our data confirm that maladaptive ECM and LV chamber remodeling is attenuated by VSMC transplantation despite limited cell engraftment. The poor cell retention after VSMC transplantation has created challenging conditions to directly implicate transplant cell paracrine mechanisms in the consistently observed beneficial effects on post MI chamber remodeling. As a proof of concept, to further assess the influence of VSMC paracrine mediators and establish ECM-dependent paracrine mechanisms, we employed an in vitro model of matricellular interaction and ECM remodeling. Our data support a novel mechanism whereby VSMC transplantation attenuates post MI structural remodeling through a preservation of ECM homeostasis.

Persistent myofibroblast activity during late stages of remodeling is maladaptive.9,24 In response to tissue injury, increased TGFβ1 and other profibrotic cytokines induce
normally quiescent fibroblasts to convert to an invasive myofibroblast phenotype. Myofibroblast-mediated ECM dysregulation results in progressive LV dilatation and systolic dysfunction. Importantly, we found that VSMC transplantation reduced myofibroblasts and limited structural remodeling in the post MI setting. While TGFβ1 expression was unchanged, bFGF expression was increased significantly after VSMC transplantation. Our in vitro data demonstrate that bFGF is capable of suppressing TGFβ1-induced fibroblast conversion to contractile myofibroblasts, and prior studies are confirmatory of this pathway. In support of our in vivo observations, Suzuki and coworkers observed bFGF to inhibit myofibroblast differentiation, limit progressive fibrosis, and suppress structural remodeling in hypertensive rats. Virag and coinvestigators determined a critical role for bFGF on fibroblast regulation and post MI remodeling using mutant mice. We show for the first time that VSMC transplantation can suppress cardiac myofibroblast differentiation and limit structural remodeling through a putative bFGF-dependent paracrine mechanism.

The profile of myocardial expression of MMP and TIMP species in the post MI heart is highly regulated within distinct spatial and temporal windows. TIMP-2 expression is elevated early after MI and then decreases during the late remodeling phase. Accordingly, our observation of enhanced TIMP-2 expression during the late phases of post MI remodeling (2 weeks and later) after cell therapy may help to control excessive MMP-2 activity, and in so doing, reduce fibroblast proliferation and activation. Importantly, reduction of collagen matrix turnover through TIMP-mediated MMP inhibition can limit progressive LV dilatation after MI. These studies suggest that VSMC-induced expression of TIMP-2 may, in addition to bFGF-mediated fibroblast inhibition, contribute to the observed reduction in maladaptive ECM and chamber remodeling.

The cellular source of enhanced TIMP-2 expression after cell therapy was not determined by this study. Interestingly, Allaire and colleagues documented VSMC to be a rich source of local TIMP production, resulting in favorable ECM regulation and stability of vascular tissue architecture. Singla and McDonald determined that embryonic stem cells inhibited apoptosis by secreting TIMP proteins. Resident cardiac fibroblasts constitutively express TIMP-2, and we speculate that these cells may serve as an additional source of production.

The specific role of cardiac TIMP proteins is as complex as they are multifunctional, and retain biological activities independent of their MMP-inhibitory capacity. As an example, while primarily an inhibitor, TIMP-2 also plays a critical role in the activation of MMP-2. We previously demonstrated in mutant mice that TIMP deficiency can cause progressive chamber remodeling without an inciting myocardial injury such as infarction. Kandalam and colleagues implicated deficient TIMP-2 as a direct cause of maladaptive post MI structural remodeling. In addition, TIMP expression has been associated with fibroblast activation and fibrosis.

Figure 5. Extracellular matrix regulation. A. Gelatin zymography showed no significant difference in MMP-2 (pro and active) expression and activity in cell transplanted hearts, as compared with controls (+ indicates MMP-2 standard control). Left ventricular myocardium was sampled from the infarction border zone. B. Quenched fluorescent assay examined the capacity for inhibition of MMP-2. Shown is a representative sample reaction profile from each group that reflects MMP-2-mediated fluorogenic substrate degradation over time. VSMC inhibited MMP-2 activity significantly more than controls, with an effect comparable with TIMP-2 (20 ng). C. By analysis of reaction slope, VSMC hearts (N=11) had a significantly higher inhibitory effect on MMP-2. *P=0.045. D. By Western blotting, TIMP-2 expression was elevated significantly in VSMC hearts as compared with controls. *P=0.01. E. Representative confocal micrographs showing enhanced TIMP-2 expression in the border zone of VSMC-transplanted hearts. Red indicates TIMP-2; blue, DAPI stained nuclei; baseline, no MMP-2 activity; VSMC, vascular smooth muscle cells; CON, medium-injected control group; MMP, matrix metalloproteinase; TIMP, tissue inhibitors of matrix metalloproteinase.
While seemingly paradoxical, myocardial fibrosis and concomitant ECM turnover frequently coexist and serve as hallmarks of progressive LV dilatation and pump failure. It is likely that the amount, duration, and timing of enhanced TIMP expression will determine whether the resultant myocardial response is adaptive or maladaptive. Interestingly, we observed that TIMP-2 induced collagen gel contraction, but the effect was suppressed by bFGF during TGFβ1 stimulation. These data support the findings of reduced fibroblast activation despite TIMP-2 increases. Further work will be necessary to determine the complex role of differential TIMP expression on fibroblast and ECM regulation, with respect to coordinating post MI structural remodeling.

Conclusion

In conclusion, cell transplantation predictably can limit maladaptive ventricular remodeling through multiple paracrine mechanisms. While cardiac regeneration remains the ultimate aim for this novel therapy, the antiremodeling abilities of cell transplantation could be harnessed to complement our contemporary surgical approaches for patients with cardiac dysfunction at risk of congestive heart failure. Efforts should continue to define mechanisms that underlie cell transplantation with a view to optimizing this technique for clinical applications.

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Disclosures

None.
References


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CLINICAL PERSPECTIVE

Structural ventricular remodeling influences the clinical progression of heart failure and has emerged as an important target for the development of novel medical and surgical therapeutic strategies. After myocardial infarction, extracellular matrix regulation plays a critical role in coordinating structural remodeling and the transition to congestive heart failure over time. Cell transplantation is an innovative biological therapy that alters the structural remodeling response in failing hearts. Paracrine mediators are released in host myocardium after cell injection and likely mediate many of the beneficial effects observed on structural remodeling. We explored the effects of cell therapy on extracellular matrix regulation and structural cardiac remodeling after myocardial infarction in a rodent model. Our data suggest that cell transplantation attenuates myocardial fibrosis and improves cardiac function. Preserving extracellular matrix homeostasis after myocardial infarction with novel cell-based therapies may limit or delay the late transition to congestive heart failure.
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