Chapter 8
Acute Myocardial Infarction, Cardioprotection, and Muse Cells

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Abstract Acute myocardial infarction (AMI) is a common cause of morbidity and mortality worldwide. Severe MI leads to heart failure due to a marked loss of functional cardiomyocytes. First-line treatment for AMI is to reperfuse the occluded coronary artery by PCI as soon as possible. Besides PCI, there are several therapies to reduce the infarct size and improve the cardiac function and remodeling. These are drug therapies such as pharmacological pre- and postconditioning, cytokine therapies, and stem cell therapies. None of these therapies have been clinically developed as a standard treatment for AMI. Among many cell sources for stem cell therapies, the Muse cell is an endogenous non-tumorigenic pluripotent stem cell, which is able to differentiate into cells of all three germ layers from a single cell, suggesting that the Muse cell is a potential cell source for regenerative medicine. Endogenous Muse cell dynamics in the acute phase plays an important role in the prognosis of AMI patients; AMI patients with a higher number of Muse cells in the peripheral blood in the acute phase show more favorable improvement of the cardiac function and remodeling in the chronic phase, suggesting their innate reparative function for the heart. Intravenously administered exogenous Muse cells engrafted preferentially and efficiently to infarct border areas via the S1P-S1PR2 axis and differentiated spontaneously into working cardiomyocytes and vessels, showed paracrine effects, markedly reduced the myocardial infarct size, and delivered long-lasting improvement of the cardiac function and remodeling for 6 months. These findings suggest that Muse cells are reparative stem cells, and thus their clinical application is warranted.

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8.1 Introduction

Acute myocardial infarction (AMI) is one of the leading causes of morbidity and mortality [1]. AMI occurs due to the total occlusion of the coronary artery mainly caused by plaque rupture. From the onset of coronary occlusion, the death of myocardial tissues spreads from the endocardial site to epicardial site over time. This is called the wave front phenomenon [2]. Therefore, if the occluded coronary artery is reperfused during the very early phase of coronary occlusion, the death of myocardial tissue will be limited to the endocardial site, the myocardial infarct size will be reduced, and the cardiac function will not be deteriorated. In the clinical setting, it has been clearly established that there is a close relationship between the time to treatment with percutaneous coronary intervention (PCI) and clinical outcome: the shorter the time to reperfusion, the better the clinical outcome [3]. Therefore, the best treatment for AMI is to reperfuse the occluded coronary artery by PCI as soon as possible to salvage the remaining viable cardiomyocytes in the myocardial tissues. However, if treatment fails to reperfuse the occluded coronary artery, or the time to reperfusion is not early enough to salvage the myocardial tissue, the myocardial infarction will become transmural from the endocardial to epicardial sites, and the infarct size will be enlarged. A large myocardial infarction usually results in the loss of a large number of cardiomyocytes, and the necrotic cardiac tissue is eventually replaced by scar formation. The wall thickness of the left ventricle (LV) will be thin and the end-diastolic LV dimension will be enlarged. This change of LV is called "LV remodeling." LV remodeling will be accelerated, and heart failure will progress, leading to a poor prognosis. Although the optimal method to treat the AMI is to reperfuse the occluded coronary artery as soon as possible, as mentioned above, the number of AMI patients whose occluded coronary artery is reperfused by PCI within 90 min from the onset time of AMI, the time duration considered to minimize cardiac damage, is quite low. Therefore, because the time from the onset of AMI to reperfusion is generally longer than 90 min in most cases, treatment in addition to PCI to protect, repair, and regenerate the heart is essential. Realistically, additional treatment will be novel and advanced therapies such as pharmacological intervention and cytokine and/or stem cell therapies.

In this review, several therapies for AMI other than PCI are described, focusing mainly on Muse cell therapy. In particular, the important role of Muse cells in the acute phase of AMI and the use of bone marrow-derived Muse cells for the treatment of AMI are described.

8.2 Pharmacological Intervention

In 1986, Murry CE et al. reported that four repetitions of a short-period coronary ischemia and reperfusion promoted resistance to subsequent prolonged coronary ischemia and markedly reduced the myocardial infarct size in dogs [4]. They named this phenomenon ischemic preconditioning (PC). Thereafter, the PC phenomenon has been noted in the rat [5], rabbit [6], and pig [7] and even in humans [8]. Patients with AMI preceded by anginal attack showed smaller infarct sizes and a better cardiac function in the chronic phase when compared with those without pre-infarct ischemia [9, 10]. Several possible mechanisms by which PC reduces the infarct size have been described. The mechanisms by which PC reduces the infarct size involve adenosine [6, 11], bradykinin [12], opioid [13], noradrenalin [14–16], free radical [17], activation of protein kinase C [18], and the opening of sarcolemmal and mitochondrial KATP channels [19, 20]. Among the abovementioned mechanisms of PC, only the KATP channel opener nicorandil is clinically available. The IONA study demonstrated that the use of KATP channel opener nicorandil significantly decreases the rate of coronary heart disease death, nonfatal MI, or unplanned hospitalization for cardiac chest pain in high-risk patients with angina pectoris [21]. However, nicorandil is effective only when prescribed before the onset of AMI.

Besides PC, Zhao et al. demonstrated that repetitive 5-min ischemia and 5-min reperfusion applied during reperfusion immediately after 60 min of coronary occlusion significantly reduced myocardial infarction [22]. This phenomenon was termed ischemic postconditioning. Ischemic postconditioning was effective in reducing the myocardial infarct size. The mechanisms by which ischemic postconditioning reduces the myocardial infarct size have been reported as activation of the reperfusion injury salvage kinase (RISK) pathway, an active effect via activation of PI3K-Akt or ERK1/2, and phosphorylation of downstream targets such as eNOS producing NO, which inhibits the opening of the mitochondrial permeability transition pore (mPTP) [23]. However, pharmacological intervention involving the mechanism of ischemic postconditioning has not yet been used clinically.

8.3 Cytokine Therapy

The granulocyte colony-stimulating factor (G-CSF), which can mobilize multipotential progenitor cells from the bone marrow (BM) into peripheral blood, has been reported to reduce the myocardial infarct size and improve postinfarction left ventricular (LV) remodeling and function [24–26]. At present, proposed mechanisms by which G-CSF causes cardioprotection are transdifferentiation of subpopulation of BM progenitor cells into cardiac tissues such as cardiomyocytes, vascular endothelial cells, vascular α-smooth muscle actin, and myofibroblasts [25, 27], acceleration of the healing process [25], and the prevention of apoptotic cardiomyocytes [26]. On the basis of animal experiments on G-CSF in acute myocardial infarction, many clinical trials have been performed [28–34]. The safety of using G-CSF for

patients with acute myocardial infarction has been confirmed in these clinical trials. Some groups reported that G-CSF is beneficial for treating patients with acute myocardial infarction, but other groups reported no beneficial effects. These differences in the efficacy of G-CSF might have been caused by differences in the doses, timing, and duration of G-CSF use and patient selection. Despite numerous clinical trials, G-CSF has not yet become a standard therapy for acute myocardial infarction.

Erythropoietin (EPO) stimulates the proliferation of early erythroid precursors and the differentiation of later precursors of the erythroid lineage [35]. Recombinant human EPO is currently used frequently in the treatment of anemia associated with end-stage renal disease [36]. Recent studies have suggested that EPO also exerts a cardioprotective effect after acute myocardial infarction (MI) [37, 38]. Although many clinical trials on EPO in acute myocardial infarction have been performed [39], EPO is considered to have no clinical benefit for heart function, reducing infarct size, cardiovascular events, or all-cause mortality. EPO has not yet become a standard therapy for acute myocardial infarction.

8.4 Human AMI and Behavior of Muse Cells in the Peripheral Blood

It has been reported that there is a baseline level of Muse cells circulating in the peripheral blood, and their number increases in stroke patients in the acute phase [40]. However, the dynamics of Muse cells in the peripheral blood in patients with AMI had not been clarified until recently [41]. We examined whether endogenous Muse cells are mobilized after AMI and whether the increase of Muse cells in the peripheral blood correlate with improvement of LV function and attenuation of LV remodeling in the chronic phase at 6 months after AMI.

We defined peripheral blood-Muse cells as $SSEA3^+$ and $CD105^+$ double-positive cells. In 79 patients with AMI, 44 patients with coronary artery disease (CAD), and 64 normal subjects (control), we measured the number of Muse cells in the peripheral blood by FACS. Muse cells were measured on days 0, 1, 7, 14, and 21 after AMI. Plasma sphingosine-1-phosphate (S1P) levels were also measured. Cardiac echocardiography was performed in the acute (within 7 days) and chronic (6 months) phases of AMI. The Muse cell number was significantly higher in the AMI patients at the acute phase within 14 days after the onset of AMI than in the CAD patients and control subjects. While day 0, the date of admission, did not show difference between AMI and CAD/control groups, the number of Muse cells peaked on day 1 and gradually decreased on days 14 and 21, returning to the baseline level. The number of Muse cells positively correlated with plasma S1P levels, and S1P elevation in the blood proceeded the increase of Muse cell number, suggesting that S1P mobilizes endogenous Muse cells into the peripheral blood.

Patients with a greater increase in the number of Muse cells in the peripheral blood in the acute phase showed an improvement of the LV function, represented by recovery of ejection fraction, and attenuation of LV remodeling, represented by left

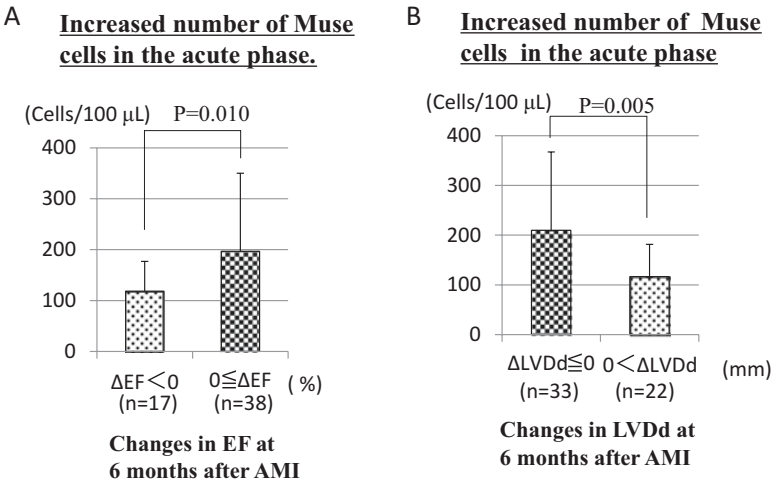

Fig. 8.1 (**A**) Increases in Muse cell numbers in the acute phase in response to AMI in patients with improved EF (ΔEF ≥ 0) or deteriorated EF (ΔEF < 0) and (**B**) attenuated LV remodeling (ΔLVDd < 0) or accelerated LV remodeling (ΔLVDd ≥0) at 6 months after AMI (Modified from Ref. [41]). AMI patients with a higher number of Muse cells in the peripheral blood showed an improvement of EF and attenuation of LV remodeling, while those with a lower number of Muse cells showed a deterioration of EF and worsening of LV remodeling

ventricle end-systolic dimension, in the chronic phase at 6 months after AMI (Fig. 8.1A). However, those with a lower increase level in the number of Muse cells in the peripheral blood showed a deterioration of the LV function and acceleration of LV remodeling in the chronic phase (Fig. 8.1B) [41]. Our study demonstrated that (1) endogenous Muse cells are mobilized into the peripheral blood, following to the elevation of blood S1P level after AMI, and (2) since the increase of peripheral blood-Muse cell number in the acute phase positively correlated with functional recovery and avoidance of heart failure, the number of peripheral blood-Muse cells could be a prognostic indicator in patients with AMI. These results also suggest that Muse cells in the peripheral blood function as reparative stem cells, and Muse cells are mobilized in response to an emergency such as AMI and repair the infarcted cardiac tissue in patients with AMI. A conceptual figure of the behavior of endogenous Muse cells in AMI is shown in Fig. 8.2.

8.5 Muse Cells as a Promising Source for Stem Cell Therapy

In large AMI, extensive tissue damage and loss of functional cardiomyocytes lead to heart failure. Therefore, stem/progenitor cell therapy to replenish cardiac tissue component such as cardiomyocytes and vessels is a fundamental medical treatment for AMI. Many stem cell types have been intensively studied for this purpose. Although

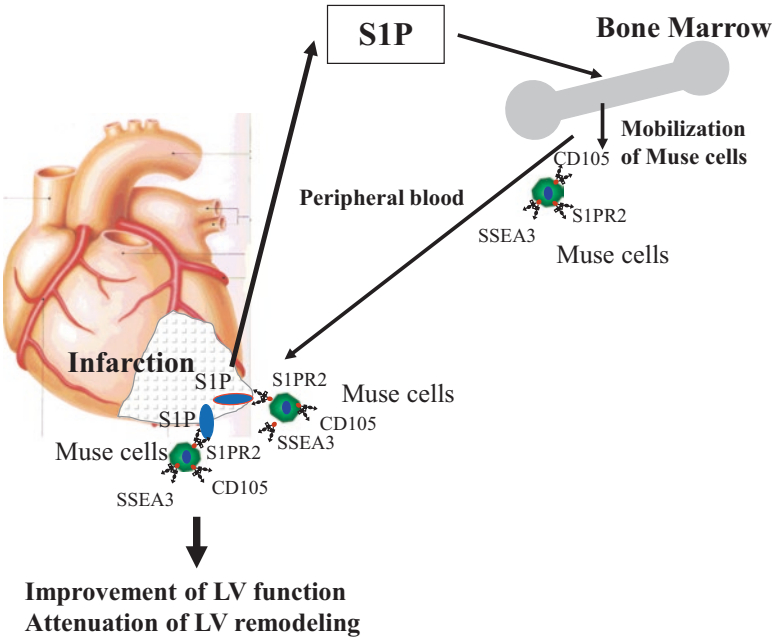

Fig. 8.2 Conceptual figure of endogenous Muse cells behavior in AMI

bone marrow (BM)-mesenchymal stem cells (MSCs) and BM-mononucleated cells (MNCs) have been successfully applied in clinical studies and their safety has been demonstrated, these cells are not clinically relevant [42, 43].

Muse cells can be harvested from the BM, connective tissue of various organs, and peripheral blood as pluripotent surface marker SSEA-3-positive [44–47]. Muse cells make up approximately 0.03% of the mononucleated fraction of the BM, and thus ~30 mL of fresh human BM aspirate yields ~0.15 million Muse cells, which expand to ~one million cells after 3 days in culture [44, 47]. Muse cells express factors related to stress tolerance and pluripotency, are self-renewable, and are able to differentiate into cells of all three germ layers from a single cell in vitro [44, 48].

We recently reported that intravenously administered Muse cells reduce the myocardial infarct size, improve left ventricular function, and attenuate LV remodeling in a rabbit AMI model [49]. AMI model was made in rabbits because rabbits have minimal collateral circulation. Japanese white rabbits underwent 30 min of coronary artery occlusion and reperfusion under anesthesia. Twenty-four hours after the onset of AMI, the rabbits were injected with autologous 3×10^5 of Muse cells/2 mL of saline (Muse group), 3×10^5 of non-Muse cells/2 mL of saline (cells other than Muse cells in MSCs; non-Muse group), or 3×10^5 of BM-MSCs (MSC group) into an ear vein and then followed up for 2 weeks or 2 months. The 2 mL of saline was intravenously injected in the vehicle group. Allograft Muse cells and human xenograft Muse cells at 3×10^5 of cells were also injected and followed up for 2 weeks without using immunosuppressive drugs. The effect of an S1PR2 antagonist on the integration of allograft Muse cells was also evaluated. For the

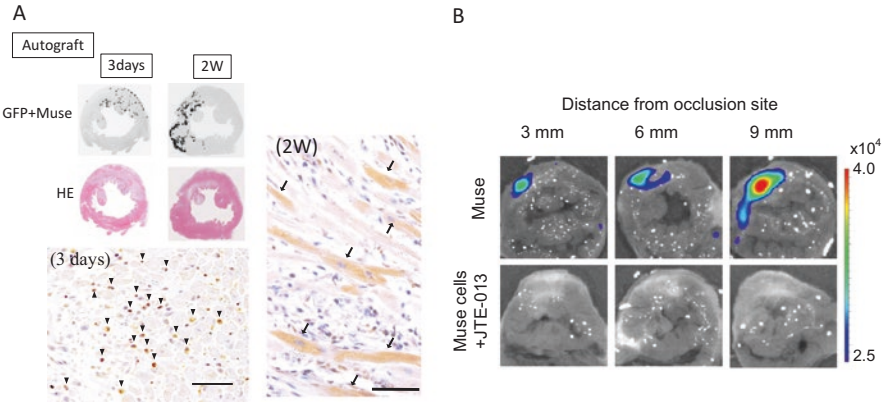

Fig. 8.3 Engraftment of Muse cells into the post-infarct heart. (**A**) Muse cells are labeled with GFP. Engraftment of Muse cells was detected by anti-GFP immunostaining at day 3 and 2 weeks. (**B**) Muse cells are labeled with Nano-lantern. Note that at 2 weeks, Muse cells selectively homed to the infarct area in the AMI heart, while their integration was substantially abrogated when JTE-013, specific antagonist of S1P receptor 2, was co-injected with Muse cells. The suppression of Muse cell homing by JTE-013 suggested that Muse cell migration and homing is mainly controlled by S1P-S1P receptor 2 axis. (Pictures adapted and modified with permission from Yamada et al. (2018), *Cir Res* [49])

6-month experiment, 3×10^5 of allograft Muse cells and vehicle (saline) were intravenously injected and evaluated at 6 months after AMI.

One of the marked characteristics of Muse cells is the high engraftment rate (~14%) of the injected cells to the infarct and infarct border areas of the heart (Fig. 8.3A). Different from the behavior of Muse cells, the other cell types such as MSCs have shown a low or zero engraftment rate when intravenously administered in papers reported previously [50, 51]. The high rate of engraftment of Muse cells to the infarct and infarct border areas is mediated by the S1P-S1PR2 axis; an interaction between S1P produced in the damaged heart and S1P receptor 2 (S1PR2) located on Muse cells [49]. Nano-lantern-labeled Muse cells demonstrated engraftment into the infarct and infarct border areas. This engraftment was completely abolished by a specific S1PR2 antagonist JTE-013 (Fig. 8.3B), suggesting that the engraftment of Muse cells is mediated mainly through S1P-S1PR2 axis.

The intravenous administration of autograft Muse cells after AMI strikingly reduced the myocardial infarct size, improved the left ventricular (LV) function, and attenuated LV remodeling at 2 months after AMI (Fig. 8.4) [49]. The myocardial infarct size was ~52% smaller as compared to the vehicle group.

Autograft, allograft, and human GFP-labeled Muse cells homed to the infarct and infarct border areas of the myocardium. These cells expressed the cardiac markers ANP, troponin I, and α-actinin and expressed vascular endothelial marker CD31 and vascular smooth muscle marker α-smooth muscle actin, suggesting that Muse cells transdifferentiated into cardiomyocytes and vessels spontaneously after engraftment (Fig. 8.5A, B, C, D, E). GCaMP-Muse cell-derived cardiomyocytes also exhibited increased GCaMP3 fluorescence during systole and decreased fluo-

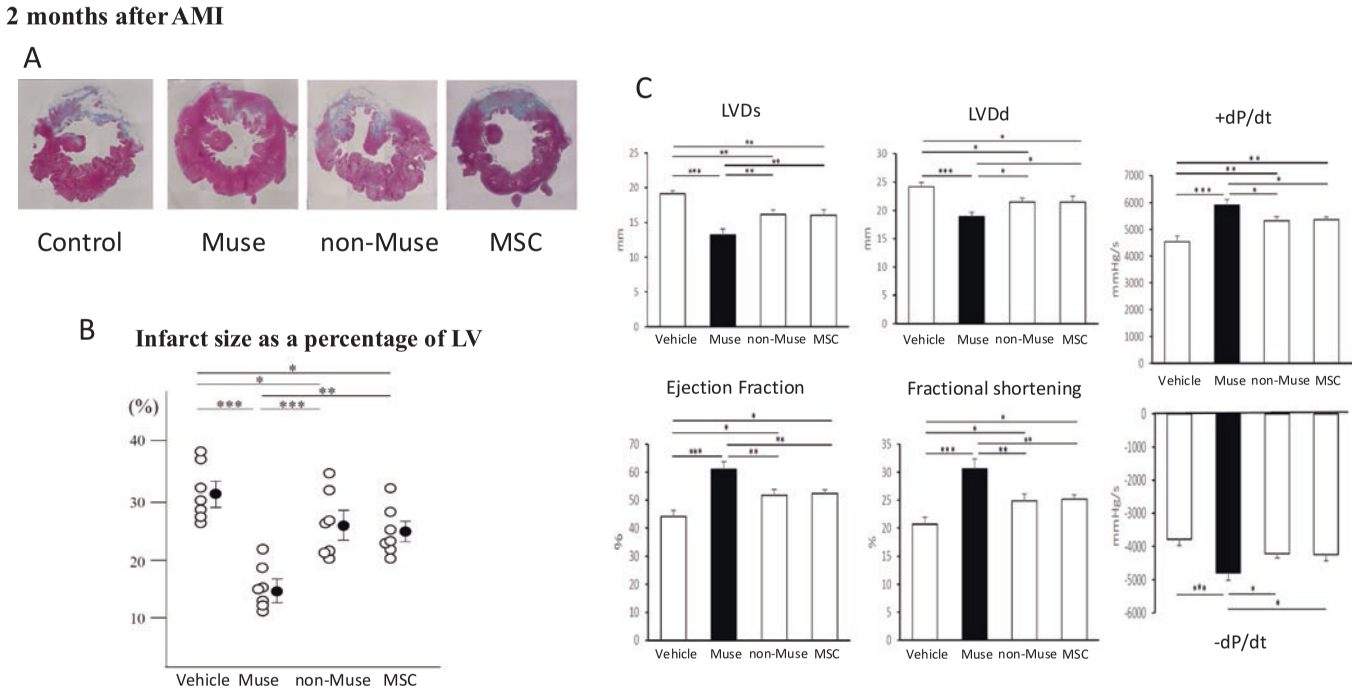

Fig. 8.4 Infarct size reduction and cardiac function recovery by Muse cell injection at 2 months. Autograft Muse cells were intravenously injected and evaluated at 2 months. (**A**) Masson-trichrome staining of LV showed the substantial reduction of infarct area (blue) in the Muse group compared to the other three groups. (**B**) The measurement of infarct size. The Muse group showed ~51% reduction in infarct size compared to the vehicle group. (**C**) Cardiac function demonstrated the substantial recovery of ejection fraction and LVDd with statistical significant differences. (Pictures adapted and modified with permission from Yamada et al. (2018), *Cir Res* [49])

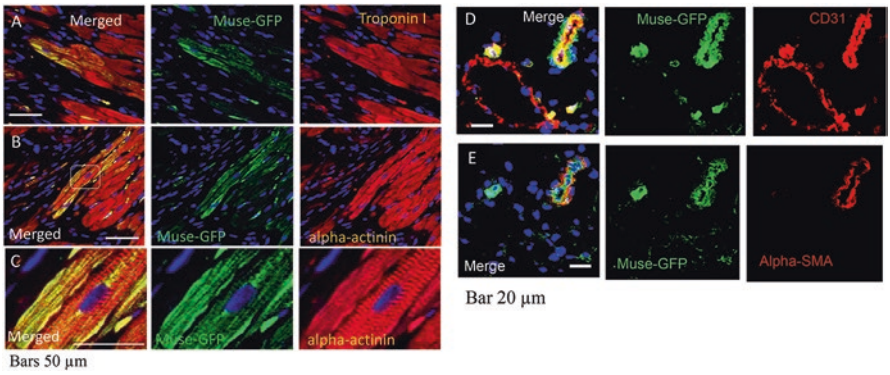

Fig. 8.5 Immunohistochemistry for cardiac troponin-I (**A**) and sarcomeric α-actinin (**B**) at 2 months. Striation-like arrangement of α-actinin (**B**) (box) is enlarged (**C**). Muse cells also spontaneously differentiated into vascular cells at 2 weeks. They expressed CD31 (**D**) and alpha-smooth muscle actin (SMA) (**E**). Bars; A–C = 50 μm; D, E = 20 μm. (Pictures adapted and modified with permission from Yamada et al. (2018), *Cir Res* [49])

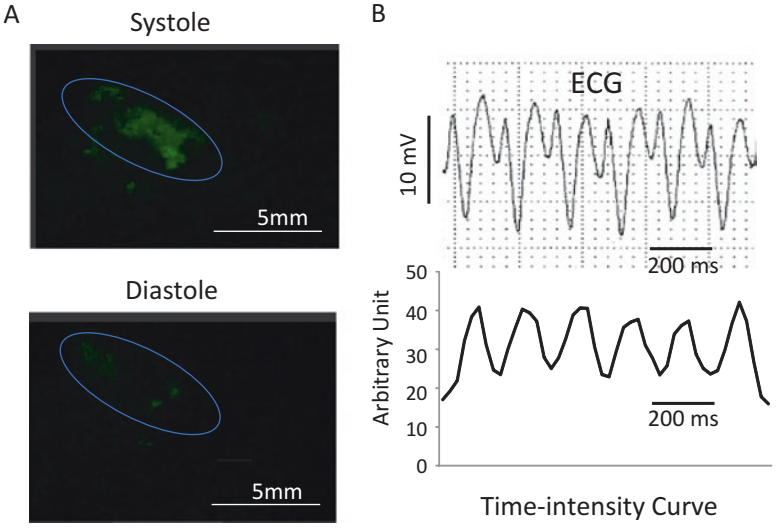

Fig. 8.6 GCaMP3-Muse cell activity in vivo. (**A**) In vivo image of GCaMP3 fluorescence in systole and diastole. (**B**) Electrocardiogram and time-intensity curve of GCaMP3 fluorescence (Pictures adapted and modified with permission from Yamada et al. (2018), *Cir Res* [49])

rescence during diastole, synchronous to electrocardiogram. This suggested that Muse cells differentiated into working cardiomyocytes with physiologic activity (Fig. 8.6A, B).

The beneficial effects of Muse cells, namely, recovery of cardiac function, reduction of infarct size, attenuation of cardiac remodeling, and suppression of fibrosis, lasted for up to 6 months after AMI in the allograft Muse cell experiment (Fig. 8.7).

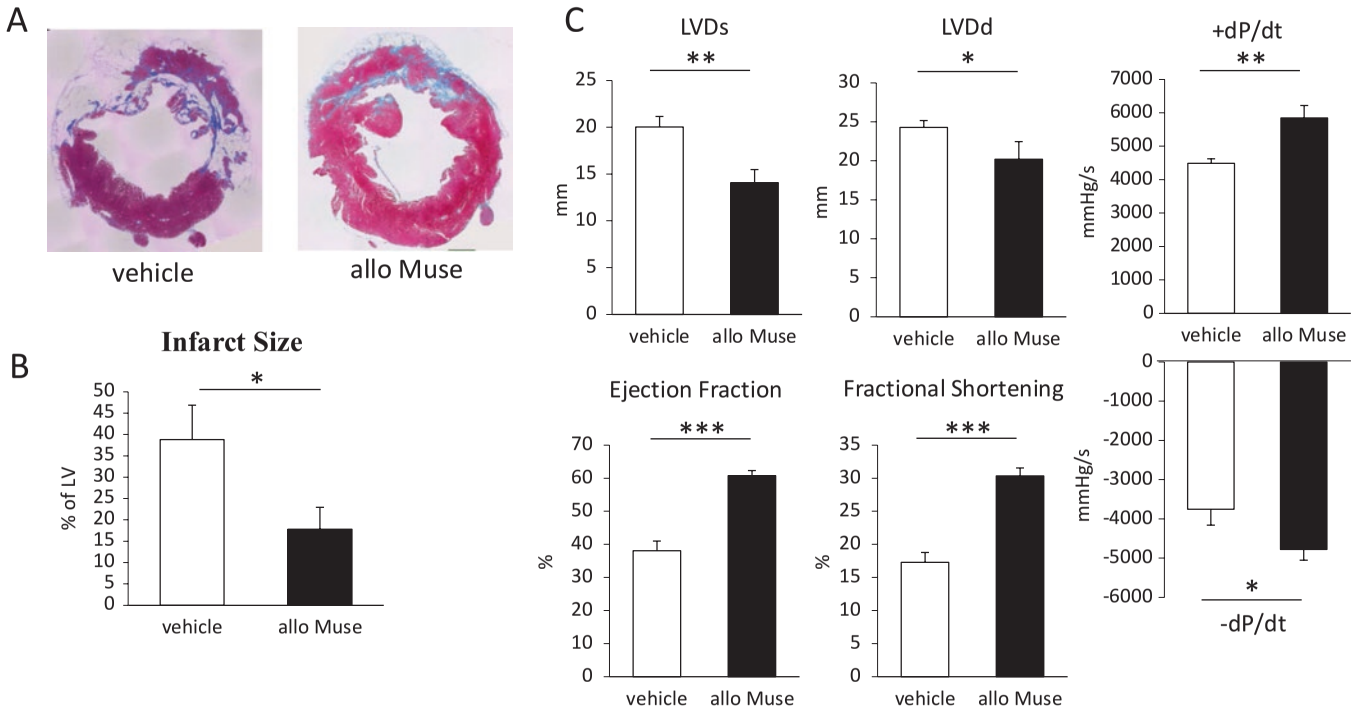

Fig. 8.7 Maintenance of the reduced infarct size and functional recovery at 6 months after intravenous injection of allogenic Muse cells. (**A**) Masson-trichrome staining and (**B**) infarct size at 6 months. (**C**) Cardiac function

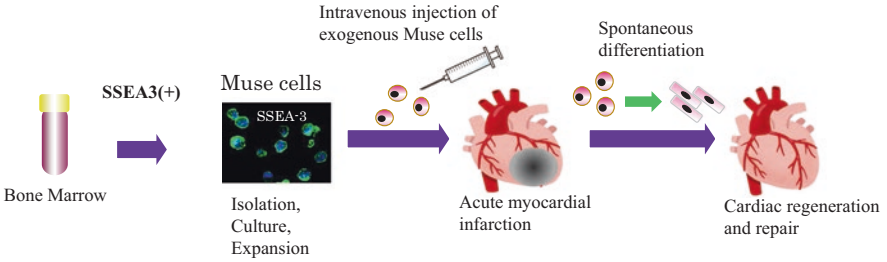

Fig. 8.8 Conceptual figure of stem cell therapy using exogenous Muse cells for the treatment of AMI

Muse cells show paracrine effects such as the production of antifibrosis/fibrinolysis factors MMP-2 and MMP-9 and trophic factors HGF and VEGF, which might have contributed to the reduction in the infarct size, through the degradation of fibrosis, anti-apoptosis, stimulation of endogenous cardiac progenitors, and neovascularization. Importantly, Muse cells not only demonstrated immunomodulatory effect similar to MSCs, i.e., conversion of naïve T cells to regulatory T cells, suppression of the differentiation of monocytes into monocyte-dendritic cell progenitors and into monocyte-dendritic cells, but ~90% of Muse cells expressed HLA-G, an immunotolerance factor expressed in the placenta during pregnancy [49]. GFP-labeled allograft Muse cells that had engrafted to the infarct border area expressed HLA-G on day 3 after AMI. These results suggest the immunotolerance and immunomodulatory effect of Muse cells [49].

All these multiple pleiotropic effects of Muse cells might have contributed to the structural and functional recovery of the heart after AMI.

A conceptual figure of cell therapy using exogenous Muse cells for the treatment of AMI is shown in Fig. 8.8.

8.6 Conclusion

After the onset of AMI, coronary reperfusion therapy by PCI is the first-line therapy to rescue the remaining viable cardiomyocytes. However, if treatment fails to reperfuse the occluded coronary artery or in long time passes until reperfusion, and consequently the infarct size is large and cardiac function is deteriorated, one of the best therapies after treatment with PCI would be regenerative therapy to reconstruct the infarcted cardiac tissue. Muse cell therapy may be a promising fundamental and epoch-making stem cell therapy for the treatment of AMI.

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