stem cells have been thoroughly examined as cell sources mainly for the treatment of heart failure following myocardial infarction. Not only cardiomyocytes derived from pluripotent stem cells, but also adult stem cells such as bone marrow stem cells or skeletal myoblasts have shown beneficial effects when transplanted into infarcted hearts. The majority of transplanted adult stem cells do not survive or transdifferentiate into cardiomyocytes, but work indirectly through the production of paracrine factors that promote endogenous repair mechanisms. Kamata et al utilized this paracrine mechanism to modulate the immune system in a rat model of autoimmune myocarditis (Figure). They previously established induced adipocyte cells by treating adipose tissue-derived stromal vascular fraction (SVF) cells from the subcutaneous fat tissue with insulin, dexamethasone, pioglitazone, and isobutylmethylxanthine. They also found that the induced adipocyte cell-sheet (iACS) can deliver a variety of cardioprotective factors, including adiponectin (APN) and hepatocyte growth factor (HGF), when transplanted into the heart in vivo; therefore, they tested if the transplantation of iACS can induce immune tolerance and functional recovery in a rat model of autoimmune-associated myocarditis. Kamata et al first compared the expression levels

Myocarditis, defined as mononuclear inflammation of the heart with damage to adjacent cardiomyocytes, is a major cause of sudden death in adolescent and young generations. Although in most cases the cause of myocarditis is idiopathic, prior viral infection such as coxsackie virus infection has been shown to be associated with the disease. Most patients recover spontaneously from acute viral myocarditis, but approximately 10% progress to chronic myocarditis. Because many chronic myocarditis patients develop autoantibodies against cardiac tissue, the autoimmune mechanism is thought to play an important role in the development of chronic myocarditis and subsequent dilated cardiomyopathy. Immunomodulatory therapies, including high-dose intravenous immunoglobulins, immunoadsorption, and immunosuppression, have been attempted, but standardized therapy has yet to be established.

In this issue of the Journal, Dr. Sawa’s team, a leading group in the field of cardiac regeneration, proposes a novel immunomodulatory therapy using a cell-sheet approach. In an attempt to regenerate the heart, both pluripotent and adult stem cells have been thoroughly examined as cell sources mainly for the treatment of heart failure following myocardial infarction. Not only cardiomyocytes derived from pluripotent stem cells, but also adult stem cells such as bone marrow stem cells or skeletal myoblasts have shown beneficial effects when transplanted into infarcted hearts. The majority of transplanted adult stem cells do not survive or transdifferentiate into cardiomyocytes, but work indirectly through the production of paracrine factors that promote endogenous repair mechanisms. Kamata et al utilized this paracrine mechanism to modulate the immune system in a rat model of autoimmune myocarditis (Figure). They previously established induced adipocyte cells by treating adipose tissue-derived stromal vascular fraction (SVF) cells from the subcutaneous fat tissue with insulin, dexamethasone, pioglitazone, and isobutylmethylxanthine. They also found that the induced adipocyte cell-sheet (iACS) can deliver a variety of cardioprotective factors, including adiponectin (APN) and hepatocyte growth factor (HGF), when transplanted into the heart in vivo; therefore, they tested if the transplantation of iACS can induce immune tolerance and functional recovery in a rat model of autoimmune-associated myocarditis. Kamata et al first compared the expression levels

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of cytokines derived from the iACS and the SVF cell-sheet (SVFSC) and found that the iACS secreted a greater amount of APN than did the SVFSC. To clarify whether APN works directly on CD4+ T cells, they confirmed the existence of 2 types of APN receptors, AdipoR1 and AdipoR2, on CD4+ T cells by reverse transcription polymerase chain reaction. They then confirmed the anti-inflammatory effects of iACS by in vitro T-cell proliferation assay. The proliferation of CD4+ T cells derived from experimental autoimmune myocarditis (EAM) rats was enhanced by adding porcine heart myosin, but this proliferation was partially inhibited by addition of either APN or HGF. The T-cell proliferation was almost completely inhibited by the addition of the supernatant of the iACS, together with decreased expression of inflammatory cytokines, indicating that the iACS expressed anti-inflammatory factors directly targeting CD4+ T cells. The authors then evaluated the activity of the iACS in a rat EAM model in vivo. When the iACS was transplanted onto the left ventricular anterior surface in EAM rats, the iACS graft area gradually decreased but survived in situ until 42 days post-transplantation. Consistent with the in vitro cytokine expression, the expression level of APN significantly increased in the iACS-transplanted hearts compared with that in the SVFSC- or sham-treated hearts.

Histological analysis revealed that infiltration of macrophages and CD4+ lymphocytes was inhibited, but the ratio of Foxp3 regulatory T cells to CD4+ T cells increased in the iACS-transplanted hearts compared with that in the SVFSC- or sham-treated hearts. Interestingly, the iACS-transplanted hearts showed a smaller myocyte diameter, indicating an antihypertrophic effect possibly through APN, and less fibrosis than in the SVFSC or sham-treated hearts. As a result, the severity of myocarditis was the lowest in the recipients of iACS-transplanted hearts compared with that in the recipients of SVFSC- or sham-treated rats according to the semi-quantitative myocarditis severity score. Note that these histological changes were ubiquitously observed in the iACS-transplanted hearts, although the transplanted iACS was localized only to the surface of the left ventricular anterior wall. The authors speculate that the epicardial host myocardium stimulated by the transplanted iACS played multiple roles in these ubiquitous effects, including indirect and/or direct mechanisms possibly through epicardial cardiac progenitor cells.

Finally, the authors evaluated the cardiac functional consequences following the transplantation. The echocardiogram showed preserved left ventricular ejection fraction and regional wall motion index in the iACS recipients compared with the SVFSC recipients and sham-treated animals. The intracardiac pressure study with conductance catheter revealed that the endystolic pressure-volume relationship, dP/dt max, and –dP/dt min were significantly greater in the iACS recipients than in the other animals.

Consistent with the findings of the current study, prior work showed that the viral gene delivery of APN into hearts affected by autoimmune myocarditis induced immune modula-
tion and subsequent reversal of left ventricular remodeling. Compared with the viral transfection method, cell-sheet transplantation has several advantages, including eliminating concerns related to the use of viral vectors and avoiding needle injections into the host myocardium. Although some issues need to be resolved before beginning clinical application, the strategy in this study seems to be promising and provides a rationale for further development of this novel immunomodulatory therapy for myocarditis.

Disclosures

The author has nothing to disclose.

References