Myocardial infarction (MI) is a life-threatening disease, as is subsequent chronic heart failure (CHF). The progression of MI to CHF is complicated. Dysregulated autophagy during ischemia/reperfusion (I/R) injury is critical in subsequent exacerbated cardiomyocyte loss. Serious cardiomyocyte loss irreversibly affects cardiac function. Many approaches have been explored to find novel treatments. Cell transplantation using several types of progenitors and adult stem cells is an emerging strategy to preserve and recover cardiomyocyte loss due to MI and CHF.

## Cell Therapy Using Bone Marrow-Derived Mesenchymal Stem Cells (BMMSCs)

Bone marrow (BM) contains mesenchymal stem cells (MSCs), which possess proliferative and multi-differentiative potentials. BMMSCs additionally have various functions that can contribute to tissue regeneration, such as immune regulation, promotion of angiogenesis, and secretion of tissue protective factors. Many preclinical and clinical...
trials using BM-derived cells have focused on ischemic heart disease and HF. Recent meta-analyses highlighted the significant concrete benefit of cell therapy on cardiac function for MI and CHF, with a 4-9% increase in the ejection fraction. Although the benefits and long-term safety of cell therapy have been established, a more efficient cell therapy strategy is desirable. Two major approaches (boosting and identification of the mechanism) seek to address this goal (Figure). The boosting strategy is attractive and focuses on improvement of cell engraftment, graft regenerative capacity, and efficacy through novel techniques. Mechanism identification is also fundamental for the development of safe and effective cell therapy. Detailed studies of the mechanisms of regeneration induced by cell therapy can lead to improved cell therapy, or even alternative therapies for cell injection. We believe that this approach would result in better modification of current cell therapy.

**Autophagy as a Novel Target of Cell Therapy**
Several preclinical studies have demonstrated that the main mechanism of MSCs in the repair of damaged heart tissue is secretion of favorable factors for the remaining cardiomyocytes, and not transdifferentiation into cardiomyocytes. Of the various molecules secreted by MSCs, secretion of exosomes has emerged as a novel and important mechanism. Of the various molecules secreted by MSCs, secretion of exosomes has emerged as a novel and important mechanism. As an example, MSC-derived exosomes reduced infarct size in a mouse model of I/R injury. Although the cardioprotective capacity of exosomes is attractive, the detailed mechanism remains unclear.

In this issue of the Journal, Li et al. describe a novel mechanism for the exosomal effects of BM-MSCs. Because appropriate autophagy is essential to prevent cardiomyocyte loss during MI, the authors tested whether BM-MSC-exosomes would prevent excess autophagy and therefore induce beneficial effects following I/R injury. Autophagy is a cellular catabolic process characterized by 2 major actions: degradation and recycling. Autophagy degrades long-lived proteins or damaged organelles by lysosomes, yielding ATP as a source of energy. An appropriate extent of autophagy is essential to maintain cellular homeostasis. However, MI and I/R injury can exacerbate autophagy in cardiomyocytes, leading to cardiomyocyte death and worsened cardiac performance in the future. Therefore, regulation of autophagy is an emerging strategy for severe ischemic heart disease.

**Multiple Effects of microRNA-29c (miR-29c)**
Li et al identified miR-29c as a specific constituent of exosomes released from BM-MSCs and demonstrated that miR-29c could alleviate cardiac damage induced by I/R injury by inhibiting excess autophagy, as assessed by examining the autophagy-related proteins LC3 and p62. miR-29c has been widely studied for malignant tumors because of its many antitumor effects. Regulation of autophagy by miR-29c, which was discovered in a study of the chemosensitivity of tumor cells, is a relatively new function for this miR. The data provided by Li et al add miR-29c as a tool in cardiac and stem cell research regarding autophagy regulation. Importantly, miR-29c also plays a role in the regulation of tissue inflammation. As is now widely recognized, regulation of the inflammatory process critically influences recovery and remodeling from ischemic damage. Comprehensive research on miR-29c might provide novel insights and effective treatments for the rescue of cardiomyocytes from extensive MI.

In summary, the efficacy of BM-MSC therapy for MI and CHF is promising but needs to be improved. The novel mechanism of BM-MSCs on the heart reported by Li et al should inform the development of multiple approaches to improving current cell therapy. Further investigations of miR-29c and autophagy regulation induced by BM-MSCs could be important for better targeted cell therapy for the heart.

**Disclosures**
The authors report no relationships that could be construed as conflicts of interest.

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