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ANGIOTENSIN RECEPTOR TYPE 2 STIMULATION INCREASES THE MIGRATION OF BONE-MARROW MONONUCLEAR CELLS INTO THE INFARCTED MYOCARDIUM AND IMPROVES HEART FUNCTION

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Objectives Stem cell therapy is a potential option for treating myocardial infarction. However, the effect is not as well as we

expected. As a matter of fact, cell therapy is faced a lot of challenges, such as poor survival of the transplanted cells in the infracted region, low number of cells migrated into myocardial lesions, and so on. So the aim of this study is to explore a new strategy that angiotensin receptor type 2 stimulation can improve the engraftment of bone marrow mononuclear cells in the infracted myocardium and recover heart function.

Methods Mononuclear cells (MNCs), isolated from SD rat bone marrow, were treated with several reagents which can change the activity of AT2R of MNCs. The experiment group designation for in vitro study were: MNCs (control), MNCs+AngII, MNCs +CGP42112A, MNCs+AngII+ARB, MNCs+AngII+PD123319 and MNCs+CGP+ARB. The ability of migration and cardioprotection were examined by tran-swell and co-culturing with neonatal cardiomyocytes. The experiment group designation for in vivo study were: DMEM, MNCs, MNCs+CGP42112A and MNCs +AngII+ARB. Cells from different groups were intramyocardially injected into the peri-infarct region. Inflammatory cytokine expression, death of cardiomyocyte, anti-apoptotic protein expression were assessed 3 days after transplantation. Meanwhile we transplant above-mentioned female rats'cells into male rats via tail vein, and evaluate the number of engrafted cells 1 day after transplantation by real-time PCR. Infarct size, angiogenesis and heart function were measured 1 month after transplantation.

Results Bone marrow mononuclear cells, when their AT2R were stimulated, can prevent neonatal cardiomyocytes from apoptosis in vitro. Also more cells migrated into low chamber in same situation. Transplantation of AT2R-activated bone marrow cells intramyocardially after myocardial infarction resulted in decrease in inflammatory cytokines (IL-1, IL-6, MCP-1) expression, death rate of cardiomyocytes in peri-infarcted region, as well as increase in anti-apoptotic protein expression (Bcl2). Also more bone marrow mononuclear cells were found in myocardial lesions 1 d after transplantation via tail vein. No matter which transplanted routes we choose, transplantation of AT2R-activated bone marrow cells can improve heart function significantly.

Conclusions Angiotensin receptor type 2 stimulation can increase the migration of bone-marrow mononuclear cells into the infracted myocardium and prevent cardiomyocytes from apoptosis, thus activate AT2R of bone marrow stem cells maybe a novel option for enhancing benefits of stem cell therapy.