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ALLOGENEIC BONE MARROW MESENCHYMAL STEM CELLS OVER-EXPRESSING GAP JUNCTION PROTEIN CONNEXIN 43 REDUCE VENTRICULAR ARRHYTHMIAS FOLLOWING MYOCARDIAL INFARCTION IN RATS

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Background Mesenchymal stem cell transplantation is a promising new therapy to improve cardiac function after myocardial infarction (MI). The electrophysiological consequences of MSC implantation have not been systematically studied.

Objective This study strived to test if allogeneic transplantation of bone marrow mesenchymal stem cells (BMSCs) over-expressing gap junction protein conexin (Cx43) reduced ventricular arrhythmias following myocardial infarction (MI) in rats.

Methods The MSCs obtained from the bone marrow of Sprague–Dawley rats were cultured in DMEM/F12 medium. Myocardial infarction was established in adult SD male rats via anterior descending branch (LAD) ligation. The transduced allogeneic stem cells were prepared in vitro and injected intramyocardially 30 min postinfarction near the experimental infarction site. Sixty rats were randomly divided into four groups. Except for the sham group, other three groups were injected with DMEM/F12 cell culture media (DMEM/F12 group) or EGFP transfected BMSCs (EGFP group), or Cx43 transfected BMSCs (Cx43 group), respectively. Four weeks postinfarction, cardiac function was evaluated by echocardiography. Then ventricular arrhythmia (ventricular tachycardia or ventricular fibrillation) was induced by electrophysiological stimulation using a Langendorff perfusion apparatus. Electrocardiogram (ECG) was recorded when incremental pacing and programmed electrical stimulation (PES) was given and then counted the inducibility of ventricular arrhythmias. The distribution and morphology of gap junctions near the areas of myocardial infarction were observed by the transmission electron microscopy (TEM). Expression of Cx43 in myocardial cells from injected area was detected by Western blot. Expression of EGFR was monitored by fluorescence microscopy.

Results Compared with DMEM/F12 group, left ventricular ejection fraction (LEVF) was improved in rats injected with BMSC (76±6.9 vs 69.3±8.1, $p<0.05$), especially in those with BMSC over-expressing Cx43 (82.9±5.0, vs 69.3±8.1, $p<0.01$). Occurrence of ventricular arrhythmias showed no difference between EGFP group and DMEM/F12 group (7/11 vs 9/12, $p=0.091$). However, the ventricular arrhythmias was less frequent in rats injected with BMSC over-expressing Cx43 than those injected with DMEM/F12 cell culture media (4/12 vs 9/12, $p<0.01$), accompanied by increased expression of Cx43 protein and improvement of gap junction remodelling in myocardial tissue.

Conclusion This study provides strong evidence that direct allogeneic BMSC transplantation improves cardiac function following MI but does not alter the occurrence of ventricular arrhythmia in rats. Transplantation of BMSCs over-expressing Cx43 not only improves cardiac function, but significantly reduces the occurrence of ventricular arrhythmia following MI.