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Cotransplantation of human umbilical cord-derived mesenchymal stem cells and umbilical cord blood-derived CD34$^+$ cells in a rabbit model of myocardial infarction

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Abstract The objective of the study is to investigate the effect of hypoxic preconditioning on the immunomodulatory properties of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) and the effect of cotransplantation of hUC-MSCs and human umbilical cord blood (hUCB)-derived CD34$^+$ cells in a rabbit model of myocardial infarction. hUC-MSCs with or without hypoxic preconditioning by cobalt chloride were plated in a 24-well plate, and then cocultured with hUCB-CD34$^+$ cells and PBMCs for 96 h at 37 °C in a 5 % CO_2 incubator. For the negative control, hUC-MSCs were omitted. The groups were divided as follows: A1 = HP-MSCs + hUCB-CD34$^+$ cells + PBMC, A2 = hUC-MSCs + hUCB-CD34$^+$ cells + PBMC, Negative Control = hUCB-CD34$^+$ cells + PBMC. Culture supernatants of each group were collected, and the IL-10 and IFN-γ levels were measured by ELISA. A rabbit model of MI was established using a modified Fujita method. The animals were then randomized into three groups and received intramyocardial injections of 0.4 ml of PBS alone ($n = 8$, PBS group), hUC-MSCs in PBS ($n = 8$, hUC-MSCs group), or hUC-MSCs + CD34$^+$ cells in PBS ($n = 8$, Cotrans group), at four points in the infarct border zone. Echocardiography was performed at baseline, 4 weeks after MI induction, and 4 weeks after cell transplantation, respectively. Stem cell differentiation and neovascularization in the infracted area were characterized for the presence of cardiac Troponin I (cTnI) and CD31 by immunohistochemical staining, and the extent of myocardial fibrosis was evaluated by hematoxylin and eosin (H&E) and Masson's trichrome. IFN-γ was 27.00 ± 1.11, 14.20 ± 0.81, and 7.22 ± 0.14 pg/ml, and IL-10 was 31.68 ± 3.08, 61.42 ± 1.08, and 85.85 ± 1.80 pg/ml for the Control, A1 and A2 groups, respectively, which indicated that hUCB-CD34$^+$ cells induced immune reaction of peripheral blood mononuclear cells, whereas both hUC-MSCs and HP-MSCs showed an immunosuppressive effect, which, however, was attenuated by hypoxic preconditioning. The Cotrans group had less collagen deposition in the infarcted myocardium and better heart function than the hUC-MSCs or PBS group. The presence of cTnI-positive cells and CD31-positive tubular structures indicated the differentiation of stem cells into cardiomyocytes and neovascularization. The microvessel density was 12.19 ± 3.05/HP for the hUC-MSCs group and 31.63 ± 2.45/HP for the Cotrans group, respectively ($P < 0.01$). As a conclusion, both hUC-MSCs and HP-MSCs have an immunosuppressive effect on lymphocytes, which, however, can be attenuated by hypoxic preconditioning. Cotransplantation of hUC-MSCs and hUCB-CD34$^+$ cells can improve heart function and decrease collagen deposition in post-MI rabbits. Thus, a combined regimen of hUC-MSCs and hUCB-CD34$^+$ cells would be more desirable than either cells administered alone. This is most likely due to the increase of cardiomyocytes and enhanced angiogenesis in the infarcted myocardium.

Keywords Myocardial Infarction · Umbilical cord mesenchymal stem cells · Umbilical cord blood-derived CD34$^+$ Cells · Cotransplantation

Li Tong and Ma Qunxing have contributed equally to this study.

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