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Original article

Co-combination of islets with bone marrow mesenchymal stem cells promotes angiogenesis

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ABSTRACT

Background: Islet transplantation is a commonly therapeutic strategy for diabetes mellitus. However, avascular phase and the poor formation of blood vessels in the late period lead to islet allograft loss which contributed to inefficiency and short-acting of islet transplantation. Recently, to speed up new angiogenesis and increase the density of blood vessels around transplanted islets became the hotspot in research of islet transplantation.
Methods: In this study, we undergone co-combination transplantation of allogeneic islet and bone marrow mesenchymal stem cells (BM-MSCs) into non-obese diabetic (NOD) mice and investigated the influence of BM-MSCs in transplanted islet function and neovascularization.
Results: In mice of co-combination transplantation of islet with BM-MSCs, level of blood glucose was improved compared with only BM-MSCs transplanted mice; proliferation of islet cell was enhanced while apoptosis of islet cell was reduced; 2, 4, and 8 weeks post transplantation, peripheral vascular density of islet grafts were significantly more than the islet transplantation group alone; donor lymphocytic chimerism in graft was increased. In result of immunofluorescence analysis, we observed that BM-MSCs can migrate to transplanted islet, differentiate into vascular smooth muscle cells (VSMC) and vascular endothelial cells (VEC), and also secrete vascular endothelial growth factor (VEGF).
Conclusion: BM-MSCs can migrate to transplanted islet and promote neovascularization. Also, it enhanced allograft immune tolerance of islet grafts via increasing donor lymphocytic chimerism.

1. Introduction

Islet transplantation is one of the ideal methods for the treatment of type 1 diabetes [1]. However, the development of this was restricted by inefficiency and short-term of islet transplantation[2]. Islet cells with high metabolic activity, the ATP and insulin secretion requires large amounts of oxygen supply to maintain. That was the reason why only the pancreas islet volume 1–2% occupies 5–10% of blood supply of pancreas [3]. While, during transplantation, islet was separated from pancreatic tissue and blood supply was damaged. Initial transplanted islet survives depending on environmental oxygen diffusion that resulted in very low oxygen partial pressure in the center of the islets. The lack of oxygen causes islet cell necrosis and apoptosis. After islet transplantation, the vascularization was taken about 14 days [4]. However, even complete revascularization, blood supply and oxygen partial pressure in graft is obviously lower than normal pancreas islet [5]. So to speed up islets around new angiogenesis and increase the density of blood vessels after transplanted has become the hotspot in research of islet transplantation in the near future.

Mesenchymal stem cells (MSCs) are multipotent stem cells which are characterized of self-renewal and multi-directional differentiation potential and derived from a variety of organs and tissues, such as bone marrow, fat and umbilical cord [6]. In addition, MSCs also play a pivotal role in immune adjustment, tissue repair regeneration and blood vessel formation [7–9]. Its application into the treatment of ischemic diseases such as ischemic cardiomyopathy has been obtained the good curative effect [10,11]. Accumulated evidences showed that MSCs promoted the formation of new blood vessels around the transplanted islet. Taihei et al. transplanted MSCs companied with islet of Lewis rat into renal capsule of non-obese diabetic-severe combined immunodeficiency disease (NOD-SCID) mice and observed the new VSMCs generated from MSCs differentiation [12]. Ito and his colleagues found that co-transplantation of islet with MSCs into

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NOD-SCID mice not only reduced insulin administration dose but also facilitated the formation of new blood vessels on account of VGEF secretion in MSCs [13]. This was also proved in researches of Figliuzzi and Rackham C [14].

In present study, NOD mice were induced immune tolerance through receiving bone marrow transplantation and immunosuppressant, and subsequently experienced co-treatment with BM-MSCs and allogeneic islet, aiming to evaluate the assist-function of BM-MSCs on islet transplantation and neovascularization.

2. Material and methods

2.1. Animals and reagents

All mice were obtained from Department of medical experimental animals of China Medical University. Female BALB/c mice (aged 8 weeks) were used for donor of bone marrow cells and islet; female BALB/c mice (aged 4 weeks) were used for donor of BM-MSCs; NOD/Lt mice (aged 12 week) were used for transplantation

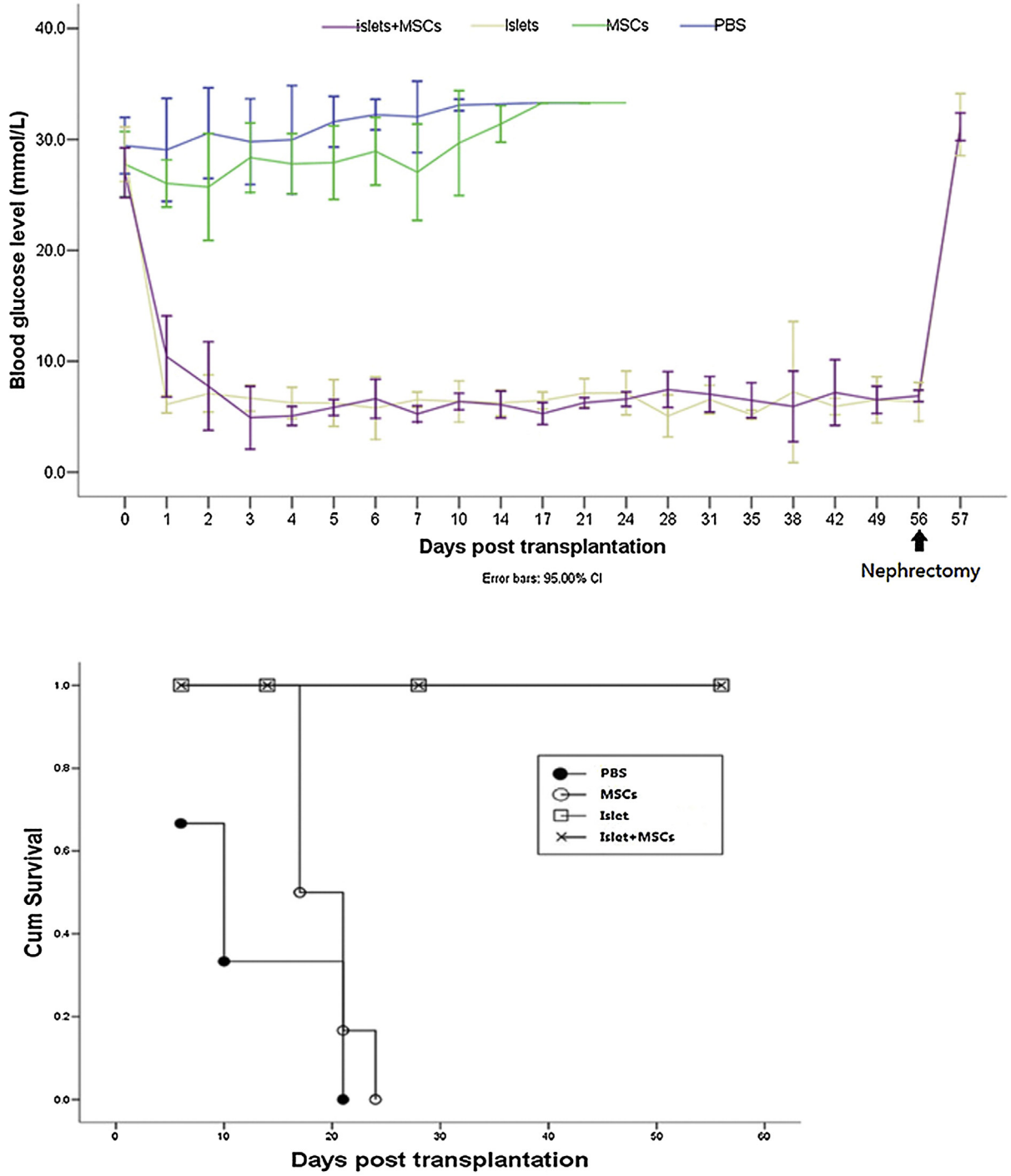

Fig. 1. Graft function. (A) Blood glucose was monitored in islet + MSCs, islet, MSCs and PBS transplanted mice for 56 days. (B) Survival curve was to evaluate viability of transplanted mice of four groups. Data were presented as mean ± s.d. $^{*}p < 0.05$ and $^{\#}p < 0.05$ compared with mice transplanted with PBS.