PROANGIOGENIC ACTIONS OF ADIPOSE TISSUE-DERIVED MESENCHYMAL STEM CELLS IN HINDLIMB ISCHEMIA MODEL

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ABSTRACT

It has been reported that adipose tissue contain progenitor cells with angiogenic potential and that therapy based on adipose tissue-derived progenitor cells administration may constitute a promising cell therapy in patients with ischemic disease. In this study we compared the effect of culture-expanded mesenchymal stem cells derived from adipose tissue (ASCs) on neovascularization and blood flow recovery in an animal model of limb ischemia in immunodeficient mice with the bone marrow stromal cells (BMSCs), and determined the proangiogenic action of ASCs isolated from diabetic rats.

ASCs were cultured from adipose tissues by collagenase digestion and BMSCs were cultured from mononuclear cells of bone marrow. Hind limb ischemia was created by ligating the proximal femoral artery of male nude mice. One day after creating hindlimb ischemia, mice were randomized to receive hASCs transplantation (hASC group), hBMSCs transplantation (hBMSCs group), or vehicle transplantation (Control group). Two weeks after transplantation, the laser Doppler perfusion index was significantly higher in the hASC group and hBMSC group than in the control group. Comparison between hASC and hBMSC group showed better recovery of blood flow in hASC group than in hBMSC group. Conditioned media from hASCs (hASC-CM) showed better in vitro tube formation of hASCs than conditioned media from hBMSCs (hBMSC-CM). hASCs showed higher expression of MMP9 than hBMSC. A MMP inhibitor, GM6001, and the transfection of MMP9 siRNA oligonucleotides inhibited in vitro tube formation of hASCs. Transplantation of MMP9 siRNA oligonucleotieds-transfected hASCs showed lower blood flow recovery and higher tissue injury than control oligonucelotide-transfected cells.

To determine the alteration of ASC function in diabetes, ASCs were isolated from the subscapular region of streptozotocin (STZ)-induced type I or high fat/STZ-induced type II diabetes rats. ASCs isolated from type I or type II diabetic rats (rASCs) showed lower proliferating ability than normal rASCs. Diabetic rASCs showed lower blood flow recovery than normal rASCs in the hindlimb ischemia model of nude mice. When ASCs isolated from

rat and human were exposed at high glucose concentration, their proliferating ability and the improvement of blood flow in hindlimb ischemia model was compromised, compared with ASCs that were maintained at normal glucose concentrations.

The data in this study indicated that ASC can be an ideal source for therapeutic angiogenesis in ischemic disease in terms of efficacy, accessibility and available tissue amounts, but the therapeutic efficacy of autologous ASCs transplantation in diabetic patients can be inferior to the expectation.

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