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Regenerative Effects of Locally or Intra-Arterially Administered BMSCs on the Thin Endometrium

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Stem cell–based therapy plays a pivotal role in the regeneration of damaged endometrium. Previous studies have demonstrated the therapeutic potential of bone marrow mesenchymal stem cells (BMSCs) through diverse administration ways. However, the homing, survival, and differentiation potential of these differently administered BMSCs are poorly defined, and the best route of administration is not well-defined. Herein, we aim to compare the engraftment, retaining time, and therapeutic efficiency of differently administered BMSCs. To achieve this, GFP/Luc-labeled BMSCs administered in two modes were assessed in a thin endometrium rat model: either into the damaged horns directly or through the ipsilateral iliac artery. The retaining time and hemi-quantitative distribution were evaluated by *in vivo* bioluminescence imaging and immunohistological analysis. Locally administered BMSCs were strongly detected in the abdomen at the first 4 days post treatment but underwent a rapid decrease in luminescent signal afterward and were rarely found 28 days after treatment. In contrast, the retaining time of BMSCs injected through the iliac artery was longer, reflected by more GFP-positive cells detected in the uterine section 28 days post treatment. Differentiation toward endometrial stromal cells was observed. Both routes of administration contributed to the restoration of the damaged endometrium, showing a comparable increase in the endometrial thickness and a decrease in fibrosis. However, more importantly, higher expression of LIF and VEGF, better recruitment, and longer retainment were found in the intra-arterial administration, contributing to the establishment of the optimal administration mode in clinical practice.

Keywords: stem cells, thin endometrium, regenerative, angiogenesis, fibrosis

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INTRODUCTION

The optimal endometrial thickness for embryo implantation is still an open issue. Thin endometrium, defined as the thickness less than 7 mm on the day of human chorionic gonadotropin (hCG) administration, is identified to be related to low implantation rates and early abortion rates (Zhang et al., 2019; Shalom-Paz et al., 2021). Various treatments have been applied to increase endometrial thickness, including hormone replacement therapy, cytokine therapy, and hysteroscopic surgery, all of which show limited efficacy on the restoration of a functional endometrium (Kamath et al., 2020). Most of the thin endometrium is caused by repeated uterine curettage–led injury and chronic inflammation of the endometrium. The functional impairment or mechanical damage is responsible for decreased endometrial regenerative activities and increased implantation failure. The loss or senescence of uterine basal layer cells might impede endometrial reconstruction (Santamaria et al., 2018; Patterson et al., 2018).