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MESENCHYMAL STROMAL CELLS

Cell type–dependent variation in paracrine potency determines therapeutic efficacy against neonatal hyperoxic lung injury

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Abstract

Background aims. The aim of this study was to determine the optimal cell type for transplantation to protect against neonatal hyperoxic lung injury. To this end, the *in vitro* and *in vivo* therapeutic efficacies and paracrine potencies of human umbilical cord blood–derived mesenchymal stromal cells (HUMs), human adipose tissue–derived mesenchymal stromal cells (HAMs) and human umbilical cord blood mononuclear cells (HMNs) were compared. *Methods.* Hyperoxic injury was induced *in vitro* in A549 cells by challenge with H_2O_2. Alternatively, hyperoxic injury was induced in newborn Sprague-Dawley rats *in vivo* by exposure to hyperoxia (90% oxygen) for 14 days. HUMs, HAMs or HMNs (5×10^5 cells) were given intratracheally at postnatal day 5. *Results.* Hyperoxia-induced increases in *in vitro* cell death and *in vivo* impaired alveolarization were significantly attenuated in both the HUM and HAM groups but not in the HMN group. Hyperoxia impaired angiogenesis, increased the cell death and pulmonary macrophages and elevated inflammatory cytokine levels. These effects were significantly decreased in the HUM group but not in the HAM or HMN groups. The levels of human vascular endothelial growth factor and hepatocyte growth factor produced by donor cells were highest in HUM group, followed by HAM group and then HMN group. *Conclusions.* HUMs exhibited the best therapeutic efficacy and paracrine potency than HAMs or HMNs in protecting against neonatal hyperoxic lung injury. These cell type-dependent variations in therapeutic efficacy might be associated or mediated with the paracrine potency of the transplanted donor cells.

Key Words: *bronchopulmonary dysplasia, cell transplantation, hepatocyte growth factor, vascular endothelial growth factor*

Introduction

Despite recent improvements in neonatal intensive care medicine [1], bronchopulmonary dysplasia (BPD), a chronic lung disease in premature infants that requires prolonged ventilatory support and oxygen supplementation, remains a major cause of mortality and long-term respiratory morbidity among premature infants [2,3]. Few effective treatments are available against BPD; therefore, the development of a new therapeutic modality to improve the outcome of this intractable disease is urgently needed.

Recently, the transplantation of various types of stem/progenitor cells has shown potential in the prevention and treatment of neonatal hyperoxic lung injury [4–9]. Of the various types of stem/progenitor cells, mesenchymal stromal cells (MSCs) are most often used in cell transplantation studies using animal models of BPD [6,9–15]. Although bone marrow (BM) is the best characterized source of MSCs, the practical use of BM is limited because of its highly invasive acquisition process [16]. Adipose tissue (AT), which can be harvested less invasively and in larger quantities than BM, is one possible alternative source of MSCs. However, the *in vivo* therapeutic efficacy of AT-derived MSCs in protecting against hyperoxic lung injury has not yet been tested. Umbilical cord blood (UCB) is considered another promising source for human MSCs because of its ready availability and the lack of significant ethical concerns. However, a long expansion time is required to obtain MSCs from UCB [17]. Thus, UCB

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mononuclear cells (MNCs), which contain high levels of primitive, multipotent stem/progenitor cells [18], might be a suitable alternative source for UCB-derived MSCs in protecting against BPD [19].

To the best of our knowledge, the therapeutic efficacies of various stem cells in protecting against neonatal hyperoxic lung injury have not yet been directly compared. The aim of the present study was to determine the best cell type for protecting against neonatal hyperoxic lung injury. To this end, the therapeutic efficacies of human UCB-derived MSCs, AT-derived MSCs and UCB MNCs in protecting against both *in vitro* and *in vivo* neonatal hyperoxic lung injury were directly compared. We also evaluated whether cell type–dependent variations in therapeutic efficacy were associated with or mediated by paracrine potency by determining the amounts of growth factors such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) produced by the transplanted donor cells.

Methods

Cell preparation

Human UCB was collected from umbilical veins after full-term newborn delivery. Informed consent was obtained from all pregnant mothers before UCB collection. From the single donor UCB, MSCs were isolated and expanded as previously described [20,21]. The differentiation potentials and immunophenotypic results of this process have also been previously described [11,20,22–24]. No changes in the karyotype was observed until 11 passages of UCB-MSCs (Supplementary Figure 1). Human AT-derived MSCs were isolated from AT that had been obtained from three adult females undergoing elective liposuction procedures. All patients provided informed consent. AT was isolated using collagenase (type I, Sigma) [25]. Fluorescence-activated cell sorter analysis revealed that both UCB-derived and AT-derived MSCs were positive for typical MSC antigens (CD73 and CD105) but negative for hematopoietic antigens (CD14, CD34 and CD45) by passage 6 (Figure 1A, Table I). To compare the differentiation potentials of the human UCB-derived MSCs and the AT-derived MSCs into mesodermal cells *in vitro*, MSCs (passage 6) were cultured in induction media for bone, cartilage and fat differentiation (Figure 1B). Both UCB-derived MSCs and AT-derived MSCs showed the potential to differentiate into bone, cartilage and fat, as evidenced by the resultant alkaline phosphatase activity, safranin O staining and numbers of lipid vacuoles, respectively. Human UCB-derived MNCs were isolated by centrifugation of UCB on a Ficoll-Hypaque gradient (density 1.077 g/cm^3, Sigma). The separated MNCs were washed and suspended as previously described [24].

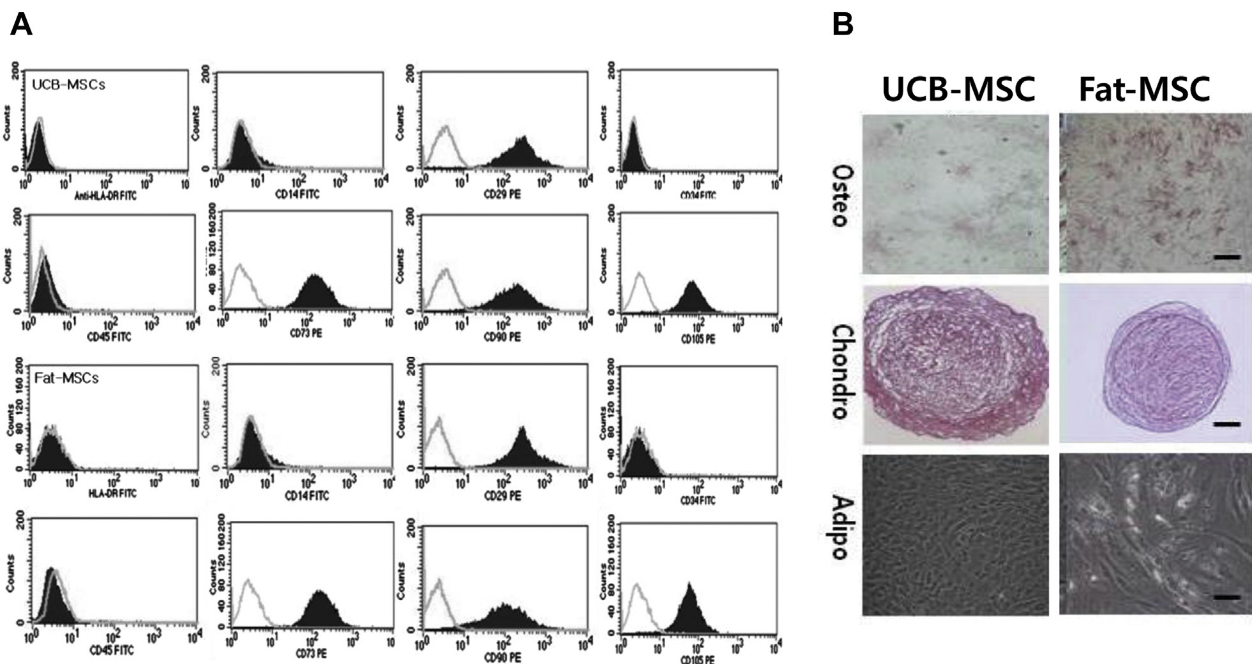

Figure 1. Comparison of the multi-lineage differentiation capacities and immunophenotypes of MSCs obtained from UCB or AT (labeled "Fat" in the figure). (A) Differentiation potentials of UCB-MSCs and AT-MSCs cultured under induction conditions. In each population, osteogenic (osteo), chondrogenic (chondro) and adipogenic (adipo) differentiation was examined by alkaline phosphatase live staining, safranin O staining and enumeration of lipid vacuoles, respectively (scale bar: 50 μm). (B) Flow cytometry analysis demonstrating the expression of various surface antigens on UCB MSCs and AT MSCs.

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