Mesenchymal Stem Cell Exosome Treatment Restores Lung Architecture And Ameliorates Pulmonary Hypertension Associated With Bronchopulmonary Dysplasia

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Rationale: With no effective treatment to prevent or reverse bronchopulmonary dysplasia (BPD), a multifactorial chronic lung disease of preterm infants, the need for new therapies is urgent. Mesenchymal stem cell (MSC)-based therapies have shown promise in numerous preclinical models of lung pathologies relevant to neonatology. We have shown that the therapeutic capacity of MSCs is comprised in their secretome, and our recent studies have demonstrated that the therapeutic vector is represented by the exosomes (extracellular vesicles; EVs) they release. Here, we aimed to purify and comprehensively characterize MSC-EVs from both human bone marrow (BMSC) and umbilical cord Wharton’s jelly (WJ) and investigate the efficacy of MSC-EV treatments in BPD.

Methods: EVs in conditioned media were isolated by density on iodixanol gradient and characterized by electron microscopy, nanoparticle tracking analysis and western blot. Proteomic profiling was obtained by LC-MS. Immunomodulatory capacity of MSC-EVs was assessed by an in vitro macrophage polarization assay. Newborn FVB mice were exposed to hyperoxia (75% O₂) for 7 days (postnatal day 1-7). At PN 4 mice were treated with a bolus intravenous dose of purified MSC-EVs or human dermal fibroblast-EVs (HDF-EVs). After hyperoxic exposure the mice were placed in room air for one to five weeks. Histological analysis of lungs harvested at PN 14 and PN 42 was performed to assess alveolar injury, blood vessel number and vascular remodeling. At PN 42, right ventricular systolic pressure (RVSP) and right ventricular hypertrophy were assessed and pulmonary function tests were conducted.

Results: EVs immunoblots were positive for CD9, TSG101 and Alix. Proteomic profiling of WJMSC-EVs and HDF-EVs detected species unique or differentially enriched in MSC-EVs. In vitro, addition of MSC-EVs to alveolar macrophages (MH-S cell line) significantly reduced the induction of M1 markers such as TNFα and CCL5. Hyperoxia-exposed mice exhibited a significantly higher mean linear intercept compared to normoxic controls or to hyperoxia-exposed mice treated with either BMSC-EVs or WJMSC-EVs, whereas HDF-EV treatment had no beneficial effect on lung architecture. Hyperoxia-exposed mice exhibited elevated RVSP compared to normoxic control mice, which was effectively reduced by treatment with BMSC-EVs or WJMSC-EVs.

Conclusion: We show that a bolus dose of purified human MSC-EVs, from two different MSC sources effectively alleviates core features of hyperoxia-induced BPD, drastically improving lung development and associated pulmonary hypertension, providing a novel platform for a new therapeutic intervention in newborn cardio-respiratory diseases.

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