AB028. Mesenchymal stem cells repair retinal vascular damage in retinopathy of prematurity mouse model

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Background: Retinopathy of prematurity is a leading cause of visual impairment and blindness in infants. Exposure of premature babies to the hyperoxic extrauterine environment leads to vaso-obliteration (VO), followed by ischemia, and subsequently pathological intravitreal neovascularization (NV) in the immature retina. Current treatments target only aberrant intravitreal vessel growth without repopulating the avascular regions of the retina. Thus, there is a dire need of new therapies that arrest pathological NV and promote normal retinal revascularization. Mesenchymal stem cells (MSCs) have shown the ability to migrate to the damaged tissue in different animal models and enhance vascularization. We, therefore, investigated whether MSCs can promote vascular repair in a mouse model of ROP.

Methods: Oxygen-induced retinopathy (OIR) model was used herein. Postnatal day 7 (P7) mice were subjected to 75% O_2 until P12 to induce VO followed by 5 days of room air leading to NV. Compact bone-derived MSCs were isolated from adult C57BL/6 mice and cultured either in hypoxia (5% O_2) or normoxia (21% O_2). Conditioned media (CM) was collected 24 hours later and injected intravitreally in P12 OIR retinas to assess vascular repair. To determine possible factors involved in MSC-induced revascularization, gene expression analysis was performed on P17 OIR retinas. *In vitro*, we investigated the effect of MSC-CM on microglial polarization using quantitative PCR and flow cytometry.

Results: Hypoxic MSC-CM significantly ($P<0.01$) decreased both VO and NV areas in comparison to the normoxic counterpart. Levels of IGF-1 and VEGF were significantly high in MSC-injected OIR retinas. Moreover, gene expression levels of pro-inflammatory cytokines (IL-1β, TNFα) dropped whereas levels of anti-inflammatory cytokines (IL-10, IL-4) increased. Treatment of pro-inflammatory M1 microglia with MSC-CM decreased the gene expression of IL-1β and TNFα, and iNOS (M1 marker) at the transcript and protein levels.

Conclusions: In this study, we demonstrated that MSCs promote healthy vessel growth in OIR retinas via a paracrine fashion by regulating expression of angiogenic factors and modulating inflammation.

Keywords: Optokinetics; visual evoked potentials; Nogo-A; 11C7

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